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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 513/06, A61K 31/435		A1	(11) International Publication Number: WO 97/40051 (43) International Publication Date: 30 October 1997 (30.10.97)
<p>(21) International Application Number: PCT/JP97/01395</p> <p>(22) International Filing Date: 23 April 1997 (23.04.97)</p> <p>(30) Priority Data: 8/102303 24 April 1996 (24.04.96) JP 8/330801 11 December 1996 (11.12.96) JP </p> <p>(71) Applicant (for all designated States except US): TAKEDA CHEMICAL INDUSTRIES, LTD. [JP/JP]; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): TAKATANI, Muneo [JP/JP]; 6-1, Taniguchisonomachi, Ukyo-ku, Kyoto-shi, Kyoto 616 (JP). SHIBOUTA, Yumiko [JP/JP]; 30-20-601, Deguchi-cho, Suita-shi, Osaka 564 (JP). SUGIYAMA, Yasuo [JP/JP]; 7-2, Daiwahigashi 5-chome, Kawanishi-shi, Hyogo 668-01 (JP). KAWAMOTO, Tetsuji [JP/JP]; 26-2-B203, Nakakidacho, Neyagawa-shi, Osaka 572 (JP).</p> <p>(74) Agents: ASAHIKA, Tadao et al.; Osaka Plant of Takeda Chemical Industries, Ltd., 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).</p>		<p>(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> </p>	
<p>(54) Title: FUSED IMIDAZOPYRIDINE DERIVATIVES AS ANTIHYPERLIPIDEMIC AGENTS</p> <p style="text-align: center;"> (I) </p> <p>(57) Abstract</p> <p>A novel compound of formula (I) wherein ring Q is an optionally substituted pyridine ring; one of R⁰, R¹ and R² is -Y⁰-Z⁰, and the other two groups are a hydrogen, a halogen, an optionally substituted hydroxy group, a hydrocarbon group that may be an optionally substituted hydrocarbon group or an acyl group; Y⁰ is a bond or an optionally substituted bivalent hydrocarbon group; Z⁰ is a basic group which may be bonded via oxygen, nitrogen, -CO-, -CS-, -SO₂N(R³)- (where R³ is hydrogen or an optionally substituted hydrocarbon group), or S(O)_n (wherein n is 0, 1 or 2); is a single bond or a double bond, or a salt thereof, which has an excellent LDL receptor up-regulating, blood-lipids lowering, blood-sugar lowering and diabetic complication-ameliorating activity.</p>			

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DESCRIPTION

FUSED IMIDAZOPYRIDINE DERIVATIVES AS ANTIHYPERLIPIDEMIC AGENTS

5

TECHNICAL FIELD

The present invention relates to novel fused imidazopyridine derivatives which are useful for prophylaxis and/or therapy of hyperlipemia, their production and use.

10

BACKGROUND ART

It has been shown by many epidemiological surveys that, alongside of hypertension and smoking, hypercholesterolemia is one of the three major risk factors for atherosclerotic diseases such as myocardial infarction, angina pectoris, and cerebral infarction. Therefore, adequate control of blood cholesterol concentration is of paramount importance for the prevention and treatment of atherosclerotic diseases such as ischemic heart diseases. As drugs for lowering cholesterol in blood, drugs which inhibit bile acid absorption by binding with bile acid, such as colestyramin and colestipol (disclosed in e.g. US Patent 4027009), drugs which inhibit acyl-CoA cholesterol O-acyltransferase (ACAT) to suppress the intestinal absorption of cholesterol, such as melinamide (disclosed in French Patent 1476569), and drugs which inhibit cholesterol biosynthesis, such as lovastatin (US Patent 4231938), simvastatin (US Patent 4231938), (US Patent 4444784), and pravastatin (US Patent 4346227), all of which are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), are attracting many attentions. However, inhibition of HMG-CoA reductase results in inhibition of not only cholesterol biosynthesis but also biosynthesis of other vital physiological substances

such as ubiquinones, dolichols, and heme A. Accordingly, these drugs are not fully satisfactory for use as medicines in view of the consequent adverse effects.

5 Meanwhile, liver low-density lipoprotein (LDL) receptors are playing a principal role in cholesterol homeostasis. Cholesterol circulating in the form of LDL is eliminated from plasma by specific LDL receptors, and taken up in the cells by the mechanism
10 of receptor-mediated intracellular uptake. Taken up in the cells, LDL particles are decomposed by the lysosomes, whereupon cholesterol is released to increase the intracellular concentration of free cholesterol. The increased free cholesterol
15 concentration transmits a signal to liver cells to lower the transcription rate of the gene of the key enzyme in the cholesterol biosynthetic pathway, and decrease biosynthesis of cholesterol. Furthermore, the LDL receptor mRNA and protein are down-regulated by
20 increased intracellular cholesterol so that the capacity of liver to eliminate the excess LDL cholesterol from plasma is compromised. Therefore, the mechanism for independent up-regulation of LDL receptors is expected to lower the plasma cholesterol
25 level still more remarkably and it is possible that any drug as up-regulating LDL receptors could be a novel hypolipemic agent.

30 Incidentally, there is not a single known compound structurally analogous to the compound of the present invention.

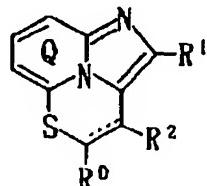
 In the above state of the art, development of a new type of antihyperlipemic drug having low-density lipoprotein (LDL) receptor up-regulating activity has been awaited.

The novel fused imidazopyridine derivatives represented by the following formula (I) have been found to possess an excellent LDL receptor up-regulating, blood-lipids lowering, blood-sugar lowering and diabetic complication-ameliorating action. And, 5 the inventors have completed the present invention.

The compound (I) of the present invention is directed to:

(1) a compound of the formula:

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wherein ring Q is an optionally substituted pyridine ring;

one of R⁰, R¹ and R² is -Y⁰-Z⁰, and the other two groups are a hydrogen, a halogen, an optionally substituted hydroxy group, an optionally substituted hydrocarbon group or an acyl group;

Y⁰ is a bond or an optionally substituted divalent hydrocarbon group;

Z⁰ is a basic group which may be bonded via oxygen, 25 nitrogen, -CO-, -CS-, -SO₂N(R³)- (wherein R³ is a hydrogen or an optionally substituted hydrocarbon group), or

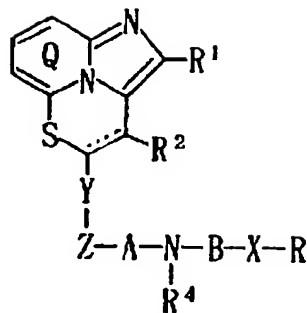
-S(O)n- (wherein n is 0, 1 or 2); and
_____ is a single bond or a double bond, or a salt thereof,

30 (2) a compound of above (1), wherein R⁰ is -Y⁰-Z⁰, wherein Y⁰ and Z⁰ are of the same meanings as defined in above (1),

(3) a compound of above (1), wherein Z⁰ is a group with a molecular weight of not greater than 1000,
35 (4) a compound of above (1) which is a compound of the

formula:

5



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wherein ring Q is an optionally substituted pyridine ring;

A and B independently are an optionally substituted divalent hydrocarbon group which may be bonded via -CON(R^{4a})-, -CO- or -N(R^{4a})-;

15 X is a bond, oxygen, sulfur, -N(R⁵)CO-, -CO(R⁵)-, -CO- or -N(R⁵)-;

Y is a bond, -CH=CH- or -CH=CH- ;

20 Z is -CO-, -COO-, -CON(R³)-, -SO₂N(R³)- or -S(O)_m- (wherein m is 0, 1 or 2);

R¹ and R² independently are a hydrogen, a halogen, an optionally substituted hydroxy group, an optionally substituted hydrocarbon group or an acyl group;

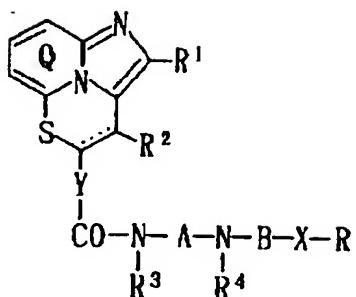
25 R³, R⁴, R^{4a} and R⁵ independently are a hydrogen or an optionally substituted hydrocarbon group; or

R³ and A, R⁴ and A, R^{4a} and B, R⁴ and R⁵, or R^{4a} and R may independently be bonded to each other to form a ring;

20 R is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; and

----- is a single bond or a double bond, or a salt thereof,

(5) a compound of above (1) which is a compound of the formula:

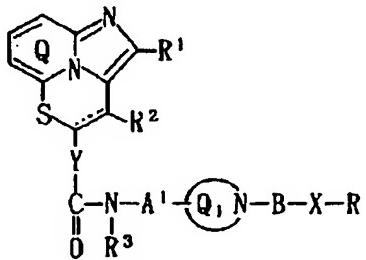


- 10 wherein ring Q is an optionally substituted pyridine ring;
 A and B independently are an optionally substituted divalent hydrocarbon group which may be bonded via -CON(R^{4a})-, -CO- or -N(R^{4a})-;
- 15 X is a bond, oxygen, sulfur, -N(R⁵)CO-, -CO(R⁵)-, -CO- or -N(R⁵)-;
 Y is a bond, -CH=CH- or -CH=CH- ;
- 20 Z is -CO-, -COO-, -CON(R³)-, -SO₂N(R³)- or -S(O)m- (wherein m is 0, 1 or 2);
 R¹ and R² independently are a hydrogen, a halogen, an optionally substituted hydroxy group, an optionally substituted hydrocarbon group or an acyl group;
- 25 R³, R⁴, R^{4a} and R⁵ independently are a hydrogen or an optionally substituted hydrocarbon group; or
 R³ and A, R⁴ and A, R⁴ and B, R⁴ and R⁵, or R⁴ and R independently may be bonded to each other to form a ring;
- 30 R is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; and
 ----- is a single bond or a double bond, or a salt thereof,
 (6) a compound of above (5), wherein A and B
- 35 independently are an alkylene group; X is a bond; and

R³ and R⁴ independently are a hydrogen or an optionally substituted alkyl, cycloalkyl, alkenyl, aralkyl or aryl group,

- (7) a compound of above (5), wherein ring Q is an unsubstituted pyridine ring; X is a bond; Y is a bond,
 OR ; A and B independently are a C₁₋₁₅ alkylene group; R¹ and R² independently are a hydrogen; R³ and R⁴ independently are a hydrogen or a C₁₋₁₅ alkyl, C₃₋₈ cycloalkyl, C₂₋₁₈ alkenyl, C₇₋₁₆ aralkyl or C₆₋₁₄ aryl group; and R is a C₆₋₁₄ aryl group,
 (8) a compound of above (1) which is a compound of the formula:

15



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wherein ring Q is an optionally substituted pyridine ring;

ring Q₁ is an optionally substituted nitrogen-containing heterocyclic ring;

A¹ is a bond or an optionally substituted divalent hydrocarbon group which may be bonded via -CON(R^{4a})-, -CO- or -N(R^{4a})-;

B is an optionally substituted divalent hydrocarbon group;

X is a bond, oxygen, sulfur, -N(R⁵)CO-, -CO(R⁵)-, -CO- or -N(R⁵)-;

Y is a bond, -CH=CH- or -CH=CH- ;

R¹ and R² independently are a hydrogen, a halogen, an optionally substituted hydroxy group, an optionally

substituted hydrocarbon group or an acyl group; R³, R^{4a} and R⁵ independently are a hydrogen or an optionally substituted hydrocarbon group; or R³ and A¹ may be bonded to each other to form a ring;

5 R is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; and _____ is a single bond or a double bond, or a salt thereof,

(9) a compound of above (8), wherein ring Q is an

10 unsubstituted pyridine ring; R¹ and R² are a hydrogen;

R³ is a hydrogen or a C₁₋₁₅ alkyl, C₃₋₈ cycloalkyl, C₂₋₁₈

alkenyl, C₇₋₁₆ aralkyl or C₆₋₁₄ aryl group; A¹ is (i) a

bond, (ii) a C₁₋₁₅ alkylene group which may be

substituted by 1 to 3 substituents selected from the

15 group consisting of hydroxy, oxo and phenyl, (iii) a C₂₋₁₆ alkenylene group or (iv) a phenylene group; B is

(i) a C₁₋₁₅ alkylene group which may be substituted by 1

to 3 substituents selected from the group consisting of

hydroxy, oxo and phenyl, (ii) a C₂₋₁₆ alkenylene group

20 or (iii) a phenylene group; ring Q₁ is a group of the formula:



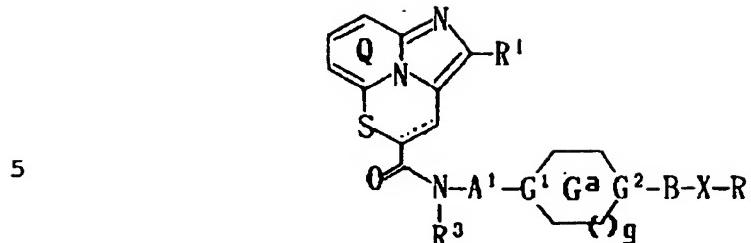
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wherein A² is =C or CH; X is a bond, oxygen, sulfur or

-CON(R⁵)-; R⁵ is a hydrogen or a C₁₋₁₅ alkyl group,

(10) a compound of above (1) which is a compound of the formula:



wherein ring Q is an optionally substituted pyridine ring;

10 A¹ is a bond or an optionally substituted divalent hydrocarbon group which may be bonded via -CON(R^{4a})-, -CO- or -N(R^{4a})-;

B is an optionally substituted divalent hydrocarbon group;

15 X is a bond, oxygen, sulfur, -N(R⁵)CO-, -CON(R⁵)-, -CO- or -N(R⁵)-;

R¹ is a hydrogen, a halogen, an optionally substituted hydroxy group, an optionally substituted hydrocarbon group or an acyl group;

20 R³, R^{4a} and R⁵ independently are a hydrogen or an optionally substituted hydrocarbon group;

R is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;
one of G¹ and G² is N, and the other is CH or N;

25 ring G^a is an optionally substituted ring;

g is 0, 1 or 2; and

_____ is a single bond or a double bond, or a salt thereof,

(11) A compound of above (10), wherein ring Q is a 30 pyridine ring which may be substituted by 1 to 3 substituents selected from the group consisting of nitro, hydroxy, cyano, carbamoyl, mono- or di-C₁₋₄ alkyl-carbamoyl, carboxy, C₁₋₄ alkoxy-carbonyl, sulfo, halogen, C₁₋₄ alkoxy, phenoxy, naphthoxy, benzyloxy, halophenoxy, C₁₋₄ alkylthio, mercapto, phenylthio,

- pyridylthio, C₁₋₄ alkylsulfinyl, phenylsulfinyl, C₁₋₄ alkylsulfonyl, phenylsulfonyl, amino, C₁₋₃ acylamino, mono- or di-C₁₋₄ alkylamino, C₁₋₄ alkyl and C₁₋₄ haloalkyl,
- 5 (12) a compound of above (10), A¹ is a bond or a C₁₋₁₅ alkylene, C₂₋₁₆ alkenylene group which may be bonded via -CON(R^{4a})-, -CO- or -N(R^{4a})-, wherein R^{4a} is of the same meaning as defined in above (10),
- (13) a compound of above (10), B is a C₁₋₁₅ alkylene or
- 10 C₂₋₁₆ alkenylene group,
- (14) a compound of above (10), X is a bond, oxygen, sulfur, -CONH- or -CO-,
- (15) a compound of above (10), R¹ is (i) a hydrogen, (ii) a halogen, (iii) a hydroxy group which may be
- 15 substituted by a C₁₋₆ alkyl, phenyl, C₇₋₁₀ aralkyl, formyl, C₁₋₆ alkyl-carbonyl, phenoxy carbonyl, C₇₋₁₀ aralkyloxy-carbonyl, pyranyl, furanyl or silyl group, (iv) a C₁₋₁₅ alkyl, C₃₋₈ cycloalkyl, C₂₋₁₈ alkenyl, C₇₋₁₆ aralkyl or C₆₋₁₄ aryl group or (v) a C₁₋₆ alkoxy-
- 20 carbonyl, mono-C₁₋₆ alkyl-carbamoyl, di-C₁₋₆ alkyl-carbamoyl or C₁₋₁₀ alkanoyl group,
- (16) a compound of above (10), R³ is a hydrogen or a C₁₋₁₅ alkyl, C₃₋₈ cycloalkyl, C₂₋₁₈ alkenyl, C₇₋₁₆ aralkyl or C₆₋₁₄ aryl group,
- 25 (17) a compound of above (10), R is (I) a C₁₋₁₅ alkyl, C₃₋₈ cycloalkyl or C₂₋₁₈ alkenyl group which may be substituted by 1 to 5 substituents selected from the group consisting of (i) nitro, (ii) hydroxy, (iii) cyano, (iv) carbamoyl, (v) mono- or di-C₁₋₄ alkyl-carbamoyl, (vi) carboxy, (vii) C₁₋₄ alkoxy-carbonyl, (viii) sulfo, (ix) halogen, (x) C₁₋₄ alkoxy, (xi) phenoxy, (xii) halophenoxy, (xiii) C₁₋₄ alkylthio, (xiv) mercapto, (xv) phenylthio, (xvi) pyridylthio, (xvii) C₁₋₄ alkylsulfinyl, (xviii) C₁₋₄ alkylsulfonyl, (xix)

amino, (xx) C₁₋₃ alkanoylamino, (xxi) mono- or di-C₁₋₄ alkylamino, (xxii) 4- to 6-membered cyclic amino, (xxiii) C₁₋₃ alkanoyl, (xxiv) benzoyl and (xxv) 5- to 10-membered heterocyclic group;

5 (II) a C₇₋₁₆ aralkyl group which may be substituted by 1 to 4 substituents selected from the group consisting of (i) halogen, (ii) C₁₋₄ alkyl, (iii) C₂₋₆ alkenyl, (iv) C₁₋₃ alkanoyl, (v) C₁₋₄ alkoxy, (vi) nitro, (vii) cyano, (viii) hydroxy, (ix) C₁₋₄ alkoxy-carbonyl, (x)

10 carbamoyl, (xi) mono- or di-C₁₋₄ alkyl-carbamoyl and (xii) mono- or di-C₂₋₄ alkenyl-carbamoyl;

(III) a C₆₋₁₄ aryl group which may be substituted by 1 to 4 substituents selected from the group consisting of (i) halogen, (ii) C₁₋₄ alkyl, (iii) C₁₋₄ haloalkyl, (iv)

15 C₁₋₄ haloalkoxy, (v) C₁₋₄ alkoxy, (vi) C₁₋₄ alkylthio, (vii) hydroxy, (viii) carboxy, (ix) cyano, (x) nitro, (xi) amino, (xii) mono- or di-C₁₋₄ alkylamino, (xiii) formyl, (xiv) mercapto, (xv) C₁₋₄ alkyl-carbonyl, (xvi) C₁₋₄ alkoxy-carbonyl, (xvii) sulfo, (xviii) C₁₋₄

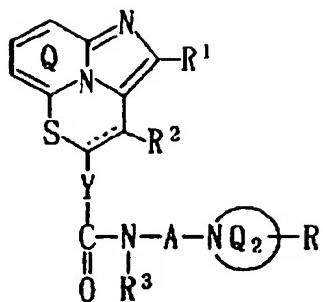
20 alkylsulfonyl, (xix) carbamoyl, (xx) mono- or di-C₁₋₄ alkyl-carbamoyl, (xxi) oxo and (xxii) thioxo; or (IV) a 5- or 6-membered monocyclic heterocyclic group containing 1 to 4 hetero-atoms selected from oxygen, sulfur and nitrogen or a fused bicyclic heterocyclic

25 group containing 1 to 6 hetero-atoms selected from oxygen, sulfur and nitrogen, each of which may be substituted by 1 to 4 substituents selected from the group consisting of (i) halogen, (ii) C₁₋₄ alkyl, (iii) C₁₋₄ haloalkyl, (iv) C₁₋₄ haloalkoxy, (v) C₁₋₄ alkoxy, (vi) C₁₋₄ alkylthio, (vii) hydroxy, (viii) carboxy, (ix)

30 cyano, (x) nitro, (xi) amino, (xii) mono- or di-C₁₋₄ alkylamino, (xiii) formyl, (xiv) mercapto, (xv) C₁₋₄ alkyl-carbonyl, (xvi) C₁₋₄ alkoxy-carbonyl, (xvii) sulfo, (xviii) C₁₋₄ alkylsulfonyl, (xix) carbamoyl, (xx)

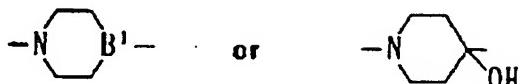
- mono- or di-C₁₋₄ alkyl-carbamoyl, (xxi) oxo and (xxii) thioxo,
- (18) a compound of above (10), wherein ring G^a is a ring which may be substituted by 1 or 2 substituents
5 selected from the group consisting of oxo and C₁₋₆ alkyl,
- (19) a compound of above (10), wherein ring Q is an unsubstituted pyridine ring; R¹ and R³ are a hydrogen; G¹ is CH; G² is N; g is 1; and R is an optionally
10 substituted hydrocarbon group or an optionally substituted heterocyclic group,
- (20) a compound of above (19), wherein ring G^a is unsubstituted ring,
- (21) a compound of above (19), wherein A¹ is a bond or
15 a C₁₋₆ alkylene group,
- (22) A compound of above (19), wherein A¹ is a bond,
- (23) A compound of above (19), wherein B is a C₁₋₆ alkylene group,
- (24) a compound of above (19), X is a bond,
20 (25) A compound of above (10), ring Q is an unsubstituted pyridine ring; R¹ and R³ are a hydrogen; A¹ is a bond; G¹ is CH; G² is N; ring G^a is a ring which may be substituted by 1 or 2 substituents selected from the group consisting of oxo and C₁₋₆ alkyl; g is 1; B is
25 a C₁₋₆ alkylene group; X is a bond; and R is an optionally substituted phenyl group,
- (26) a compound of above (25), ring G^a is unsubstituted ring,
- (27) a compound of above (25), wherein R is a phenyl
30 group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, hydroxy, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy and C₁₋₄ haloalkoxy,
- (28) a compound of above (1) which is a compound of the
35 formula:

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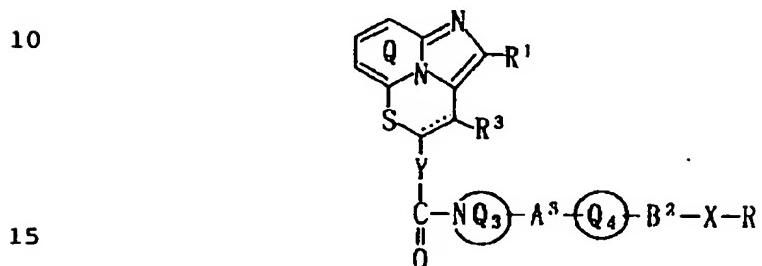
- 10 wherein ring Q is an optionally substituted pyridine ring;
 ring Q₂ is an optionally substituted nitrogen-containing heterocyclic ring;
 A is an optionally substituted divalent hydrocarbon group which may be bounded via -CON(R^{4a})-, -CO- or -N(R^{4a})-;
- 15 R¹ and R² independently are a hydrogen, a halogen, an optionally substituted hydroxy group, an optionally substituted hydrocarbon group or an acyl group;
 R³ and R^{4a} independently are a hydrogen or an optionally substituted hydrocarbon group; or
 R³ and A may be bonded to each other to form a ring;
- 20 R is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; and
 _____ is a single bond or a double bond, or a salt thereof,
- (29) a compound of above (28), wherein ring Q is an unsubstituted pyridine ring; R¹ and R² are a hydrogen; R³ is a hydrogen or a C₁₋₁₅ alkyl, C₁₋₈ cycloalkyl, C₂₋₁₈ alkenyl, C₇₋₁₆ aralkyl or C₆₋₁₄ aryl group; A is (i) a C₁₋₁₅ alkylene group which may be substituted by 1 to 3 substituents selected from the group consisting of hydroxy, oxo and phenyl, (ii) a C₂₋₁₆ alkenylene group

or (iii) a phenylene group; ring Q₂ is a group of the formula:



wherein B¹ is =C, CH or N,

(30) a compound of above (1) which is a compound of the formula:



wherein ring Q is an optionally substituted pyridine ring;

ring Q₃ and Q₄ independently are an optionally

20 substituted nitrogen-containing heterocyclic ring; A³ and B² independently are a bond or an optionally substituted divalent hydrocarbon group;

X is a bond, oxygen, sulfur, -N(R⁵)CO-, -CON(R⁵)-, -CO- or -N(R⁵)-;

25 Y is a bond, -CH=CH- or -CH=CH-  ;

R¹ and R² independently are a hydrogen, a halogen, an optionally substituted hydroxy group, an optionally substituted hydrocarbon group or an acyl group;

30 R⁵ is a hydrogen or an optionally substituted hydrocarbon group;

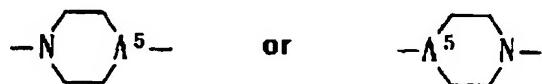
R is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; and

_____ is a single bond or a double bond, or a salt thereof,

(31) a compound of above (30), wherein ring Q is an unsubstituted pyridine ring; R¹ and R² are a hydrogen; A³ and B² independently are a bond or a C₁₋₁₅ alkylene, C₂₋₁₆ alkenylene or phenylene group; ring Q₃ is a group of the formula:



wherein A⁴ is =C or CH; ring Q₄ is a group of the formula:



15 wherein A⁵ is =C or CH,

(32) a compound of above (1) which is a compound of the formula:

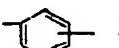


wherein ring Q is an optionally substituted pyridine ring;

30 ring Q₅ is an optionally substituted nitrogen-containing heterocyclic ring;

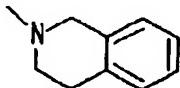
A is an optionally substituted divalent hydrocarbon group which may be bonded via -CON(R^{4a})-, -CO- or -N(R^{4a})-;

Y is a bond, -CH=CH- or -CH=CH-



R¹ and R² independently are a hydrogen, a halogen, an optionally substituted hydroxy group, an optionally substituted hydrocarbon group or an acyl group;
 R³ and R⁴^a independently are a hydrogen or an optionally substituted hydrocarbon group; and
 _____ is a single bond or a double bond, or a salt thereof,
 (33) a compound of above (32), wherein ring Q is an unsubstituted pyridine ring; R¹ and R² are a hydrogen;
 10 R³ is a hydrogen or a C₁₋₁₅ alkyl, C₃₋₈ cycloalkyl, C₂₋₁₈ alkenyl, C₇₋₁₆ aralkyl or C₆₋₁₄ aryl group; A is a C₁₋₁₅ alkylene, C₂₋₁₆ alkenylene or phenylene group; ring Q₅ is a group of the formula:

15



(34) a compound of above (1) which is (R)-N-[1-(1,4-benzodioxan-2-ylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide, or a pharmaceutically acceptable salt thereof,
 20 (35) a compound of above (1) which is N-[1-(3-phenylpropyl)piperidin-4-ylmethyl]-3-(5-thia-1,8b-diazaacenaphthylene-4-yl)acrylamide, or a pharmaceutically acceptable salt thereof,
 25 (36) a compound of above (1) which is N-[4-(4-phenylpiperidin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide, or a pharmaceutically acceptable salt thereof,
 30 (37) a compound of above (1) which is N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide, or a pharmaceutically acceptable salt thereof,

The "halogen" in this specification means fluorine, chlorine, bromine, iodine, etc.

The "hydrocarbon group" in the term "optionally

substituted hydrocarbon group" in this specification means alkyl, alkenyl, aralkyl, aryl, etc.

The "alkyl" includes "straight-chain or branched C₁₋₁₅ alkyl" such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, tridecyl, tetradecyl, pentadecyl, etc. and "C₃₋₈ cycloalkyl" such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc.

10 The substituent groups which may be substituted on said "straight-chain or branched C₁₋₁₅ alkyl and C₃₋₈ cycloalkyl" include (i) nitro, (ii) hydroxy, (iii) cyano, (iv) carbamoyl, (v) mono- or di-C₁₋₄ alkyl-carbamoyl (e.g. N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, etc.), (vi) carboxy, (vii) C₁₋₄ alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, etc.), (viii) sulfo, (ix) halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), (x) 20 C₁₋₄ alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), (xi) phenoxy, (xii) halophenoxy (e.g. o-, m- or p-chlorophenoxy, o-, m- or p-bromophenoxy, etc.), (xiii) C₁₋₄ alkylthio (e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio, etc.), (xiv) mercapto, (xv) phenylthio, (xvi) pyridylthio, (xvii) C₁₋₄ alkylsulfinyl (e.g. methylsulfinyl, ethylsulfinyl, etc.), (xviii) C₁₋₄ alkylsulfonyl (e.g. methylsulfonyl, ethylsulfonyl, etc.), (xix) amino, (xx) C₁₋₃ alkanoylamino (e.g. acetylarnino, propionylarnino, etc.), (xxi) mono- or di-C₁₋₄ alkylarnino (e.g. methylarnino, ethylarnino, dimethylarnino, diethylarnino, etc.), (xxii) 30 4- to 6-membered cyclic amino (e.g. 1-azetidinyl, 1-pyrrolidinyl, piperidino, morpholino, thiomorpholino, 1-piperazinyl, etc.), (xxiii) C₁₋₃ alkanoyl (e.g. formyl, acetyl, etc.), (xxiv) benzoyl and (xxv) 5- to

10-membered heterocyclic group (e.g. 2- or 3-thienyl; 2- or 3-furyl; 3-, 4- or 5-pyrazolyl; 2-, 4- or 5-thiazolyl; 3-, 4- or 5-isothiazolyl; 2-, 4- or 5-oxazolyl; 1,2,3- or 1,2,4-triazolyl; 1H- or 2H-tetrazolyl; 2-, 3- or 4-pyridyl; 2-, 4- or 5-pyrimidinyl; 3- or 4-pyridazinyl; quinolyl; isoquinolyl; indolyl; etc.). The "alkyl" may have 1 to 5 (preferably 1 to 3) substituents in the substitutable positions on the alkyl.

10 Preferred examples of the "alkyl" are straight-chain or branched C₁₋₆ alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc. The substituent group which may be substituted on the "C₁₋₆ alkyl" includes
15 said halogen, C₁₋₄ alkoxy, hydroxy, C₁₋₄ alkoxy-carbonyl, carboxy, carbamoyl, mono- or di-C₁₋₄ alkyl-carbamoyl, pyridylthio, etc. The number of substituents may range from 1 to 3.

20 The "alkenyl" includes "C₂₋₁₈ alkenyl" such as vinyl, allyl, isopropenyl, 3-butenyl, 3-octenyl, 9-octadecenyl, etc. The substituent groups which may be substituted on the "alkenyl" are of the same groups as the substituent groups of said "alkyl". The number of substituent groups may range from 1 to 3. Preferred
25 examples of the "alkenyl" are C₂₋₆ alkenyl groups such as vinyl, allyl, 2-butenyl, 3-butenyl, etc. The substituent groups which may be substituted on said "C₂₋₆ alkenyl" are of the same groups as the substituent groups of said "C₁₋₆ alkyl". The number of substituent groups may range from 1 to 3.

30 The "aralkyl" includes C₇₋₁₆ aralkyl, typically, phenyl-C₁₋₆ alkyl such as benzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, etc. and naphthyl-C₁₋₆ alkyl such as (1-naphthyl)methyl, 2-(1-naphthyl)ethyl, etc.
35

The substituent groups which may be substituted on said "aralkyl" include (i) halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), (ii) C₁₋₄ alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, etc.), (iii) 5 C₂₋₆ alkenyl (e.g. vinyl, allyl, 2-butenyl, 3-butenyl, etc.), (iv) C₁₋₃ alkanoyl (e.g. formyl, acetyl, etc.), (v) C₁₋₄ alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), (vi) nitro, (vii) cyano, (viii) hydroxy, (ix) C₁₋₄ alkoxy-carbonyl (e.g. 10 methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, etc.), (x) carbamoyl, (xi) mono- or di-C₁₋₄ alkyl-carbamoyl (e.g. N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, etc.) and (xii) mono- or di-C₂₋₄ 15 alkenyl-carbamoyl (e.g. N-vinylcarbamoyl etc.). The "aralkyl" may have 1 to 4 (preferably 1 to 3) substituent groups such as those mentioned above in substitutable positions on the aralkyl.

The "aryl" includes aromatic monocyclic, dicyclic 20 or tricyclic C₆₋₁₄ aryl such as phenyl, 1-naphthyl, 2-naphthyl, phenanthryl, anthryl, etc. Preferred is phenyl.

The substituent groups which may be substituted on 25 said "aryl" include (i) halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), (ii) C₁₋₄ alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, etc.), (iii) C₁₋₄ haloalkyl (e.g. trifluoromethyl, 2,2,2-trifluoroethyl, trichloromethyl, etc.), (iv) C₁₋₄ halo- 30 alkoxy (e.g. trifluoromethoxy, trichloromethoxy, 2,2,2-trifluoroethoxy), (v) C₁₋₄ alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), (vi) C₁₋₄ alkylthio (e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio, etc.), (vii) hydroxy, (viii) carboxy, (ix) cyano, (x) nitro, (xi) amino, (xii) mono- or di-C₁₋₄ 35 alkylamino (e.g. methylamino, ethylamino,

dimethylamino, diethylamino, etc.), (xiii) formyl, (xiv) mercapto, (xv) C₁₋₆ alkyl-carbonyl (e.g. acetyl, propionyl, butyryl, hexanoyl, etc.), (xvi) C₁₋₄ alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, 5 propoxycarbonyl, isopropoxycarbonyl, etc.), (xvii) sulfo, (xviii) C₁₋₄ alkylsulfonyl (e.g. methylsulfonyl, ethylsulfonyl, etc.), (xix) carbamoyl, (xx) mono- or di-C₁₋₄ alkyl-carbamoyl (e.g. N-methylcarbamoyl, N-ethylicarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, etc.), (xxi) oxo and (xxii) thioxo. The "aryl" may have 1 to 4 (preferably 1 or 2) substituent groups such as those mentioned above in substitutable positions on the aryl. The aryl having oxo group(s) includes benzoquinonyl, naphthoquinolyl, 10 anthraquinonyl, etc.

The term "acyl" in this specification includes acyl derived from carboxylic acid, such as alkoxy-carbonyl, alkyl-carbamoyl and alkanoyl.

The "alkoxy-carbonyl" includes C₁₋₆ alkoxy-carbonyl 20 such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxy-carbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, neopentyloxycarbonyl, tert-pentyloxycarbonyl, etc.

The "alkyl-carbamoyl" includes N-mono-C₁₋₆ alkyl-carbamoyl such as N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N-butylcarbamoyl, etc.; N,N-di-C₁₋₆ alkyl-carbamoyl such as N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N,N-dipropylcarbamoyl, N,N-dibutylcarbamoyl, N-ethyl-N-methylcarbamoyl, etc.; and 30 4- to 6-membered cyclic carbamoyl formed jointly by two alkyl moieties, such as 1-azetidinylcarbonyl, morpholinocarbonyl, 1-pyrrolidinylcarbonyl, 1-piperidinocarbonyl, 1-piperazinylcarbonyl, (1-piperazinylcarbonyl), etc.

The "alkanoyl" includes C₁₋₁₀ alkanoyl such as formyl and C₁₋₉, alkyl-carbonyl (e.g. acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, etc.).

5 The "acyl group" further may be substituted by 1 to 3 substituents such as the substituent groups on the above-mentioned alkyl group.

10 The "divalent hydrocarbon group" in the term "optionally substituted divalent hydrocarbon group" in this specification includes divalent acyclic hydrocarbon groups such as C₁₋₁₅ alkylene (e.g. methylene, ethylene, propylene, butylene, pentamethylene, hexamethylene, heptamethylene, octamethylene, etc.), C₂₋₁₆ alkenylene (e.g. vinylene, 15 propenylene, 1-butenylene, 2-butenylene, 1-pentenylene, 2-pentenylene, 3-pentenylene, etc.) and C₂₋₁₆ alkinylene (e.g. ethinylene, propinylene, 1-butinylene, 2-butinylene, 1-pentinylene, 2-pentinylene, 3-pentinylene, etc.), phenylene and various combinations 20 of these groups. Preferable examples of the divalent hydrocarbon groups are C₁₋₁₅ alkylene (e.g. methylene, ethylene, propylene, butylene, pentamethylene, hexamethylene, heptamethylene, octamethylene, etc.) and C₂₋₁₆ alkenylene (e.g. vinylene, propenylene, 1-butenylene, 25 2-butenylene, 1-pentenylene, 2-pentenylene, 3-pentenylene, etc.). The "divalent hydrocarbon group" may contain -CO-, -CON(R^{4a})- or -N(R^{4a})- (wherein R^{4a} represents a hydrogen or an optionally substituted hydrocarbon group) as a terminal or interrupting group.

30 The substituent groups which may be substituted on said "divalent acyclic hydrocarbon group" include an optionally substituted alkyl group, an optionally substituted aralkyl group, an optionally substituted aryl group, a hydroxy, an oxo, an amino and a halogen, 35 and preferable examples of them are an optionally

substituted alkyl group.

The "alkyl" of said "optionally substituted alkyl group substituted", the "aralkyl" of said "an optionally substituted aralkyl group", and the "aryl" of said "an optionally substituted aryl group" may be respectively the same groups as mentioned hereinbefore.

The substituent group which may be substituted on the "alkyl", "aralkyl" and "aryl" mentioned as substituents on said "divalent acyclic hydrocarbon group" may be the same groups as those mentioned as examples of the substituent group on the "optionally substituted hydrocarbon group". The number of substituents may range from 1 to 4.

The "phenylene" may be substituted. The substituent group which may be substituted on the phenylene includes (i) halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), (ii) C₁₋₄ alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, etc.), (iii) C₁₋₄ alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), (iv) C₁₋₄ alkylthio (e.g. methylthio, ethylthio, propylthio, isopropylthio, etc.), (v) hydroxy, (vi) carboxy, (vii) cyano, (viii) nitro, (ix) amino, (x) mono- or di-C₁₋₄ alkylamino (e.g. methylamino, ethylamino, dimethylamino, diethylamino, etc.), (xi) formyl, (xii) mercapto, (xiii) C₁₋₄ alkyl-carbonyl (e.g. acetyl, propionyl, butyryl, etc.), (xiv) C₁₋₄ alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, etc.), (xv) sulfo, (xvi) C₁₋₄ alkylsulfonyl (e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl, etc.), (xvii) carbamoyl and (xviii) mono- or di-C₁₋₄ alkyl-carbamoyl (e.g. N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, etc.). The number of substituents may range from 1 to 4.

The "heterocyclic group" in the term "optionally substituted heterocyclic group" in this specification

includes 5- or 6-membered monocyclic heterocyclic groups which contain 1 to 4 hetero-atoms selected from, for example, oxygen, sulfur and nitrogen, and bicyclic fused heterocyclic groups which contain 1 to 6 hetero-atoms selected from, for example, oxygen, sulfur and nitrogen.

In the above-mentioned "heterocyclic groups", the monocyclic heterocyclic group may be 5- or 6-membered monocyclic aromatic heterocyclic groups which contain 1 to 4 hetero-atoms selected from oxygen, sulfur and nitrogen and saturated or unsaturated monocyclic nonaromatic heterocyclic groups. The examples of them are thienyl (e.g. 2-thienyl, 3-thienyl, etc.), furyl (e.g. 2-furyl, 3-furyl, etc.), pyranyl, 2H-pyrrolyl, 15 pyrrolyl (e.g. 2-pyrrolyl, 3-pyrrolyl, etc.), imidazolyl (e.g. 2-imidazolyl, 4-imidazolyl, etc.), pyrazolyl (e.g. 3-pyrazolyl, 4-pyrazolyl, etc.), isothiazolyl (e.g. 3-isothiazolyl, 4-isothiazolyl, etc.), isoxazolyl (e.g. 3-isoxazolyl, 4-isoxazolyl, 20 etc.), pyridyl (e.g. 2-pyridyl, 3-pyridyl, 4-pyridyl, etc.), pyrazinyl, pyrimidinyl (e.g. 2-pyrimidinyl, 4-pyrimidinyl, etc.) and pyridazinyl (e.g. 3-pyridazinyl, 4-pyridazinyl, etc.). These monocyclic heterocyclic groups may be saturated or partially saturated, and such saturated or partially saturated monocyclic heterocyclic groups may, for example, be pyrrolidinyl (e.g. 2-pyrrolidinyl, 3-pyrrolidinyl, etc.), pyrrolinyl (e.g. 2-pyrrolin-3-yl, etc.), imidazolinyl (e.g. 2-imidazolin-4-yl, etc.), piperidyl (e.g. 2-piperidyl, 3-piperidyl, etc.), piperazinyl (e.g. 2-piperazinyl, etc.) and morpholinyl (e.g. 3-morpholinyl, etc.).

In the above-mentioned "heterocyclic group", the bicyclic fused heterocyclic group may be bicyclic fused aromatic heterocyclic groups which contain 1 to 6 hetero-atoms selected from oxygen, sulfur and nitrogen, or saturated or unsaturated bicyclic fused nonaromatic

heterocycle groups. These typical examples are benzodioxanyl (e.g. 1,4-benzodioxan-2-yl, etc.), isobenzofuranyl (e.g. 1-benzofuranyl, etc.), chromenyl (e.g. 2H-chromen-3-yl, etc.), benzothienyl (e.g. 2-benzothienyl, etc.), indolizinyl (e.g. 2-indolizinyl, 3-indolizinyl, etc.), isoindolyl (e.g. 1-isoindolyl, etc.), 3H-indolyl (e.g. 3H-indol-2-yl, etc.), indolyl (e.g. 2-indolyl, etc.), 1H-indazolyl (e.g. 1H-indazol-3-yl, etc.), purinyl (e.g. 8-purinyl, etc.), 10 isoquinolyl (e.g. 1-isoquinolyl, 3-isoquinolyl, etc.), quinolyl (e.g. 2-quinolyl, 3-quinolyl, etc.), phthalazinyl (e.g. 1-phthalazinyl, etc.), naphthyridinyl (e.g. 1,8-naphthyridin-2-yl, etc.), quinoxalinyl (e.g. 2-quinoxalinyl, etc.), quinazolinyl 15 (e.g. 2-quinazolinyl, etc.) and cinnolinyl (e.g. 3-cinnolinyl, etc.). The bicyclic fused heterocyclic group may be partially saturated, and such partially saturated bicyclic fused heterocyclic group includes isochromanyl (e.g. 3-isochromanyl, etc.), indolinyl 20 (e.g. 2-indolinyl, etc.), isoindolinyl (e.g. 1-isoindolinyl, etc.), 1,2,3,4-tetrahydro-2-quinolyl, 1,2,3,4-tetrahydro-3-isoquinolyl, etc.

The substituent group which may be substituted on said "heterocyclic group" includes the same groups as 25 those mentioned as the substituent group which may be substituted on the "aryl" in said "optionally substituted hydrocarbon group", and the number of the substituents may range from 1 to 4 (preferably 1 to 3).

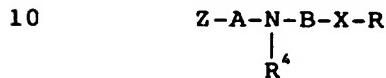
The substituent group on the "optionally 30 substituted hydroxy group" in this specification includes (i) C₁₋₆ alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), (ii) phenyl, (iii) C₇₋₁₀ aralkyl (e.g. benzyl, etc.), (iv) formyl, (v) C₁₋₆ alkyl-carbonyl (e.g. methylcarbonyl, ethylcarbonyl, etc.), (vi) phenoxy carbonyl, (vii) C₇₋₁₀ aralkyloxy carbonyl (e.g. benzyloxycarbonyl, etc.), (viii)

pyranyl, (ix) furanyl and (x) silyl, each of which may be substituted. The substituent group which may be substituted on these groups includes halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), C₁₋₄ alkyl (e.g. methyl, ethyl, propyl, isopropyl, etc.), phenyl, C₇₋₁₀ aralkyl (e.g. benzyl etc.), nitro, etc. and the number of substituents may range from 1 to 4.

The "substituent" on ring Q includes (i) nitro, (ii) hydroxy, (iii) cyano, (iv) carbamoyl, (v) mono- or di-C₁₋₄ alkyl-carbamoyl (e.g. N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, etc.), (vi) carboxy, (vii) C₁₋₄ alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, etc.), (viii) sulfo, (ix) halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), (x) C₁₋₄ alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), (xi) phenoxy, naphthoxy, benzyloxy, (xii) halophenoxy (e.g. o-, m- or p-chlorophenoxy, o-, m- or p-bromophenoxy, etc.), (xiii) C₁₋₄ alkylthio (e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio, etc), (xiv) mercapto, (xv) phenylthio, (xvi) pyridylthio, (xvii) C₁₋₄ alkylsulfinyl (e.g. methylsulfinyl, ethylsulfinyl, etc.), phenylsulfinyl, (xviii) C₁₋₄ alkylsulfonyl (e.g. methylsulfonyl, ethylsulfonyl, etc.), phenylsulfonyl, (xix) amino, (xx) C₁₋₃ acylamino (e.g. acetylamino, propionylamino, etc.), (xxi) mono- or di-C₁₋₄ alkylamino (e.g. methylamino, ethylamino, dimethylamino, diethylamino, etc.), (xxii) C₁₋₄ alkyl (e.g. methyl, ethyl, propyl, isopropyl, etc.) and (xxiii) C₁₋₄ haloalkyl (e.g. trifluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, etc.).

Ring Q may have 1 to 3 such substituents in substitutable positions on the ring Q, but is preferably unsubstituted.

The term "basic group" in this specification are, for example, (1) (i) an optionally substituted amino group and/or (ii) a group with a molecular weight of not greater than 1000 (preferably not greater than 5 300), such as a hydrocarbon group which has 1 to 10 (preferably 1 to 5) heterocyclic group(s) containing 1 to 4 hetero-atoms selected from nitrogen, oxygen and sulfur, as terminal and/or interrupting groups and (2) a group of the formula:



wherein all symbols are of the same meanings as defined hereinbefore.

15 The above-mentioned "optionally substituted amino group" includes N-mono-substituted amino and N,N-di-substituted amino.

20 The "N-mono-substituted amino" means an amino group having one substituent group, where the substituent group may, for example, be alkyl (particularly C₁₋₁₅ alkyl and C₃₋₈ cycloalkyl), aryl (particularly C₆₋₁₄ aryl), heterocyclic (particularly 5- or 6-membered monocyclic aromatic heterocyclic), and aralkyl (particularly C₇₋₁₆ aralkyl) groups as mentioned 25 above.

25 The "N,N-di-substituted amino" means an amino group having two substituent groups. One of these two substituent groups are of the same substituent groups as mentioned for "N-mono-substituted amino". The other 30 substituent group are the above-mentioned alkyl (particularly C₁₋₁₅ alkyl and C₃₋₈ cycloalkyl), aryl (particularly C₆₋₁₄ aryl) and aralkyl (particularly C₇₋₁₆ aralkyl) groups. The two substituents on the amino group may form a cyclic amino group taken together with 35 the adjacent nitrogen atom. Examples of the cyclic amino group are 1-azetizinyl, 1-pyrrolidinyl,

piperidino, morpholino, thiomorpholino; 1-piperazinyl and 1-piperazinyl having the above-mentioned alkyl (particularly C₁₋₁₅ alkyl or C₃₋₈ cycloalkyl), aryl (e.g. C₆₋₁₄ aryl) or aralkyl group (e.g. C₇₋₁₆ aralkyl) in the 5 4-position.

The "heterocyclic group which contains 1 to 4 hetero-atoms selected from nitrogen, oxygen and sulfur" includes (i) 5- or 6-membered heterocyclic groups such as imidazolyl, 2H-pyrrolyl, pyrrolyl, pyrazolyl, 10 isoxazolyl, furazanyl, pyrrolidinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, piperidinyl, thiomorpholinyl, morpholinyl, etc. and (ii) bicyclic or tricyclic fused heterocyclic groups such as 15 indolizinyl, isoindolyl, 3H-indolyl, indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, 20 phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxazinyl, indolinyl, isoindolinyl, etc.

The hydrocarbon group in the term "hydrocarbon group having 1 to 10 (preferably 1 to 5) heterocyclic group(s) containing 1 to 4 hetero-atoms selected from 25 nitrogen, oxygen and sulfur, as terminal and/or interrupting groups" may, for example, be the same group as the "optionally substituted hydrocarbon group" as mentioned above.

The "basic group" may be bonded to Y⁰ either 30 directly or via oxygen (-O-), nitrogen [-N(R³)-], carbonyl (-CO-), thiocabonyl (-CS-), -S(O)_n- (wherein n is to 0, 1 or 2), or a combination thereof: -CO-N-(R³)-, -CS-N(R³)-, -S(O)_n-N(R³)-, -COO-, -CS-O- (wherein R³ is a hydrogen or an optionally substituted 35 hydrocarbon group).

The "hydrocarbon group" and "substituent" on the

hydrocarbon group of the "optionally substituted hydrocarbon group" as mentioned for R³ include the same groups for the "optionally substituted hydrocarbon group" as mentioned hereinbefore.

5 The term "alkyl", "cycloalkyl", "alkenyl", "aralkyl", "aryl", and "substituent" on these group of the "optionally substituted alkyl, cycloalkyl, alkenyl, aralkyl or aryl group" may, for example, be the same groups as those respectively mentioned for said
10 "optionally substituted hydrocarbon group".

The ring formed jointly by R⁴ and A may, for example, be an optionally substituted heterocyclic group Q₁ which contains 1 to 4 nitrogen atoms.

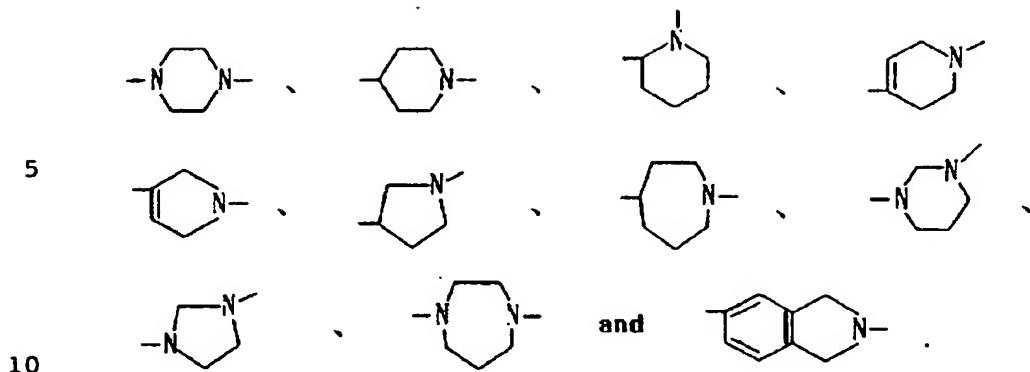
15 The ring formed jointly by R⁴ and B may, for example, be an optionally substituted heterocyclic group Q₂ which contains 1 to 4 nitrogen atoms.

The ring formed jointly by R³ and A may for example, be an optionally substituted heterocyclic group Q₃ which contains 1 to 4 nitrogen atoms.

20 The ring formed jointly by R⁴ and R⁵ may, for example, be an optionally substituted heterocyclic group Q₄ which contains 1 to 4 nitrogen atoms.

25 The ring formed jointly by R⁴ and R may, for example, be an optionally substituted heterocyclic group Q₅ which contains 1 to 4 nitrogen atoms.

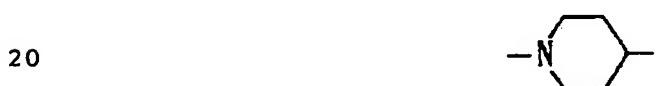
Ring Q₁ includes a group of the formula:



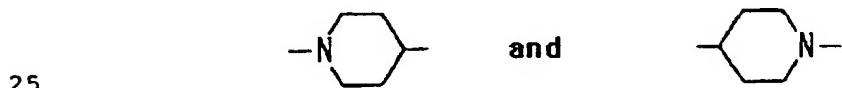
Ring Q, includes a group of the formula:



Ring Q₃ includes a group of the formula:



Ring Q₄ includes a group of the formula:



Ring O₅ includes a group of the formula:



The substituent which may be substituted on the ring Q₁, ring Q₂, ring Q₃, ring Q₄ and ring Q₅ includes the same groups as mentioned for the substituent on said "optionally substituted heterocyclic group". The number of substituents is 1 to 4.

- The protective group of the "optionally protected COOH group" in this specification includes an optionally substituted C₁₋₆ alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), phenyl, 5 trityl and silyl group, etc., each of which may be substituted by 1 to 3 substituents selected from the group consisting of halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), formyl, C₁₋₆ alkyl-carbonyl (e.g. acetyl, propionyl, butyryl, etc.) and nitro, etc.
- 10 The protective group of the "optionally protected CH₂OH group" in this specification includes an optionally substituted C₁₋₆ alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), phenyl, C₇₋₁₀ aralkyl (e.g. benzyl), formyl, C₁₋₆ alkyl-carbonyl 15 (e.g. acetyl, propionyl, butyryl, etc.), phenoxy carbonyl (e.g. benzyloxy carbonyl, etc.), C₇₋₁₀ aralkyloxy-carbonyl (e.g. benzyloxy carbonyl, etc.), pyranyl, furanyl, silyl, etc., each of which may be substituted by 1 to 4 substituents selected from the 20 group consisting of halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), C₁₋₆ alkyl (e.g. methyl, ethyl, propyl, isopropyl, etc.), phenyl, C₇₋₁₀ aralkyl (e.g. benzyl, etc.) and nitro, etc.
- 25 The "optionally protected CHO group" in this specification includes CHO, acetals such as di-C₁₋₆ alkyl acetal (e.g. dimethyl, acetal, diethyl acetal, etc.) and 1,3-dioxolane.
- Ring Q is preferably unsubstituted ring.
- R is preferably an optionally substituted C₆₋₁₄ 30 aryl group, an optionally substituted C₇₋₁₆ aralkyl group or an optionally substituted bicyclic aromatic heterocyclic or a saturated or unsaturated bicyclic nonaromatic heterocyclic group which contains 1 to 6 hetero-atoms selected from oxygen, sulfur and nitrogen.
- 35 The substituent group which may be substituted on

said "C₆₋₁₄ aryl", "bicyclic aromatic heterocyclic group" or "saturated or unsaturated bicyclic non aromatic heterocyclic group" includes the same groups mentioned as the "substituent" on the aryl as an example of the "hydrocarbon group" of said "optionally substituted hydrocarbon group" as mentioned hereinbefore. These groups may be substituted by 1 to 5 substituents as mentioned above in the substitutable positions.

The substituent group which may be substituted on said "C₇₋₁₆ aralkyl" includes the same groups mentioned for the "substituent" which may be substituted on the aralkyl as an example of the "hydrocarbon group" of said "optionally substituted hydrocarbon group", and 1 to 4 of such substituents may be substituted in the substitutable positions.

X is preferably a bond, oxygen or sulfur.

Y is preferably a bond or a group of the formula:

R¹ is preferably hydrogen, C₁₋₆ alkyl (e.g. methyl, ethyl, propyl, isopropyl, etc.) or phenyl. R² and R³ each is preferably hydrogen.

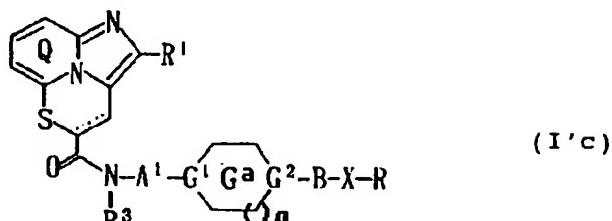
R⁴ is preferably C₁₋₁₀ alkyl (e.g. methyl, ethyl, propyl, isopropyl, etc.), or R⁴ and A, R⁴ and B, or R³ and R⁴ respectively, jointly and taken together with the adjacent nitrogen atom, form a ring. The preferred ring includes pyrrolidine, piperidine, piperazine, etc.

Preferable examples of A and B respectively are C₁₋₁₀ alkylene (e.g. methylene, ethylene, propylene, butylene, pentamethylene, hexamethylene, heptamethylene, octamethylene, etc.) or C₂₋₈ alkenylene (e.g. vinylene, propenylene, etc.). The bond between the 3- and 4-positions of the 5-thia-1,8b-diazaacenaphthylene nucleus is preferably a double

bond.

The preferred compound of the present invention includes a compound of the formula (I'c):

5



10

wherein ring Q is an optionally substituted pyridine ring;

A¹ is a bond or an optionally substituted divalent hydrocarbon group which may be bonded via -CON(R^{4a})-, -CO- or -N(R^{4a})-;

B is an optionally substituted divalent hydrocarbon group;

X is a bond, oxygen, sulfur, -N(R⁵)CO-, -CON(R⁵)-, -CO- or -N(R⁵)-;

R¹ is a hydrogen, a halogen, an optionally substituted hydroxy group, an optionally substituted hydrocarbon group or an acyl group;

R³, R^{4a} and R⁵ independently are a hydrogen or an optionally substituted hydrocarbon group;

R is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

one of G¹ and G² is N, and the other is CH or N;

ring G^a is an optionally substituted ring;

g is 0, 1 or 2; and

..... is a single bond or a double bond, or a salt thereof.

In the formula (I'c) as mentioned hereinbefore, preferred are compounds, wherein ring Q represents an unsubstituted pyridine ring; R¹ and R³ both represent a hydrogen; G¹ represents CH; G² represents N; g

represents 1; R represents an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group (both as defined hereinbefore); and the other symbols are of the same meanings as defined
5 hereinbefore. Particularly preferred are compounds, wherein ring G^a is unsubstituted ring; A¹ represents a bond or a C₁₋₆ alkylene (e.g. methylene, ethylene, propylene, butylene, pentamethylene, etc.); A¹ is more preferably a bond; B represents a C₁₋₆ alkylene (e.g.
10 methylene, ethylene, propylene, butylene, pentamethylene, etc.); and X represents a bond.

In the formula (I'c) as mentioned hereinbefore, preferred are compounds, wherein ring Q represents an unsubstituted pyridine ring; R¹ and R³ both represent a
15 hydrogen; A¹ represents a bond; G¹ represents CH; G² represents N; B represents a C₁₋₆ alkylene (e.g. methylene, ethylene, propylene, butylene, pentamethylene, etc.); X represents a bond; and R represents an optionally substituted phenyl group (the
20 substituent group(s) of the phenyl may be similar to those which may be substituted on the aryl for said hydrocarbon group). Particularly preferred are compounds, wherein ring G^a is unsubstituted ring; R represents a phenyl group which is substituted by 1 to
25 3 substituents selected from the group consisting of halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), hydroxy, C₁₋₄ alkyl (methyl, ethyl, propyl, isopropyl, butyl, etc.), C₁₋₄ haloalkyl (e.g. trifluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl,
30 etc.), C₁₋₄ alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.) and C₁₋₄ haloalkoxy (e.g. trifluoromethoxy, trichloromethoxy, 2,2,2-trifluoroethoxy, etc.), etc.

The salt of the compound (I) according to the
35 present invention is preferably a physiologically

acceptable acid additional salt. Among such salts are salts with inorganic acids (e.g. hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid, etc.) and salts with organic acids (e.g. acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid, etc.). Furthermore, in cases where the compound (I) of the present invention contains an acidic group such as carboxyl, the compound (I) may form physiologically acceptable salts with inorganic bases (e.g. alkali metal or alkaline earth metal elements such as sodium, potassium, calcium, magnesium, etc., or ammonia) or organic bases (e.g. tri-C₁-₃ alkylamines such as triethylamine).

The starting compounds for the synthesis of the compound (I) may also be used in the salt form such as the above salt, but the kind of salt is not limited unless it is detrimental to the reaction.

The compound (I) may contain a double bond within the molecule. Two kinds (Z and E) of stereoisomers in the compound (I) and the mixtures thereof fall within the scope of the present invention.

While the compound (I) may also assume enol- and keto-forms with respect to the oxo group, the respective forms as well as mixtures thereof fall within the scope of the invention.

Some species of the compound (I) have asymmetric carbon within the molecule. And two kinds (R and S) of stereoisomers in the compound (I) and the mixtures thereof fall within the scope of the invention.

The typical compounds of the compound (I) are as follows.

N-[1-(3-Phenylpropan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide and its acid additional salt.

N-[1-(3-(2-Fluorophenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide and its acid additional salt.

5 N-[1-(2-Fluorophenethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide and its acid additional salt.

N-[1-(4-Fluorophenethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide and its acid additional salt.

10 N-[1-(3-Fluorophenethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide and its acid additional salt.

N-[1-(3-(2-Chlorophenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide and its acid additional salt.

15 N-[1-(3-Chlorophenethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide and its acid additional salt.

N-[1-(2-Chlorophenethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide and its acid additional salt.

20 N-[1-(4-Chlorophenethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide and its acid additional salt.

N-[2-(1-(2-Chlorophenethyl)piperidin-4-yl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide and its acid additional salt.

30 N-(1-Phenethylpiperidin-4-ylmethyl)-5-thia-1-diazaacenaphthylene-4-carboxamide and its acid additional salt.

N-[1-(3-Phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide and its acid additional salt.

N-(1-Phenethylpiperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide and its acid additional salt.

5 N-[4-(4-Benzylpiperidin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide and its acid additional salt.

10 N-[4-(4-Phenylpiperidin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide and its acid additional salt.

15 N-[1-(1,4-Benzodioxan-2-ylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide and its acid additional salt.

20 (S)-N-[1-(1,4-Benzodioxan-2-ylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide and its acid additional salt.

25 (R)-N-[1-(1,4-Benzodioxan-2-ylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide and its acid additional salt.

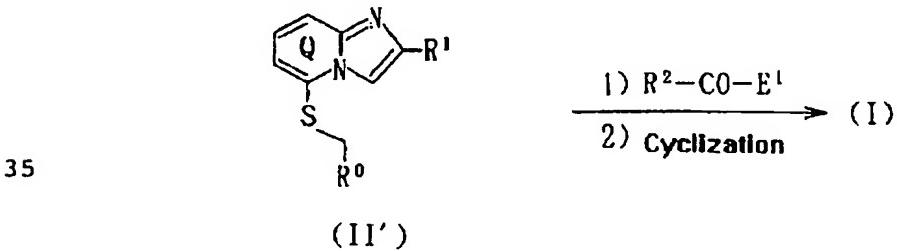
30 N-[1-(3-Phenylpropan-1-yl)piperidin-4-ylmethyl]-3-(5-thia-1,8b-diazaacenaphthylene-4-yl)acrylamide and its acid additional salt.

N-(1-Phenethylpiperidin-4-yl)-3-(5-thia-1,8b-diazaacenaphthylene-4-yl)acrylamide and its acid additional salt.

35 N-(1-Phenethylpiperidin-4-ylmethyl)-3-(5-thia-1,8b-diazaacenaphthylene-4-yl)acrylamide and its acid additional salt.

The compound (I) of the present invention can be synthesized by, for example, the following process.

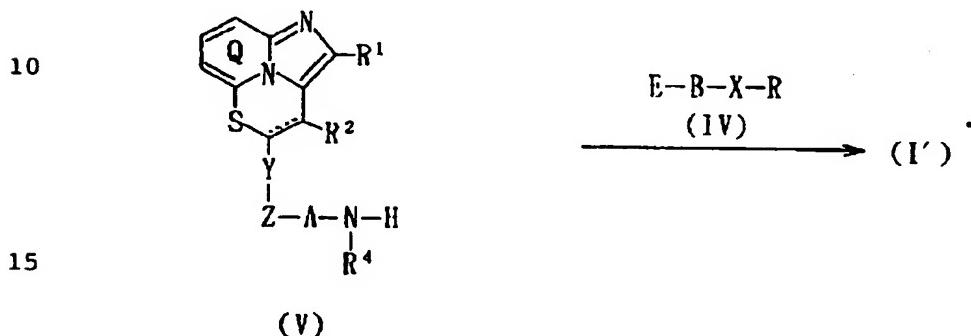
30



wherein E¹ represents halogen (e.g. chlorine) or R²CO-O- (wherein R² is of the same meaning as defined hereinbefore); and the other symbols are of the same meanings as defined hereinbefore.

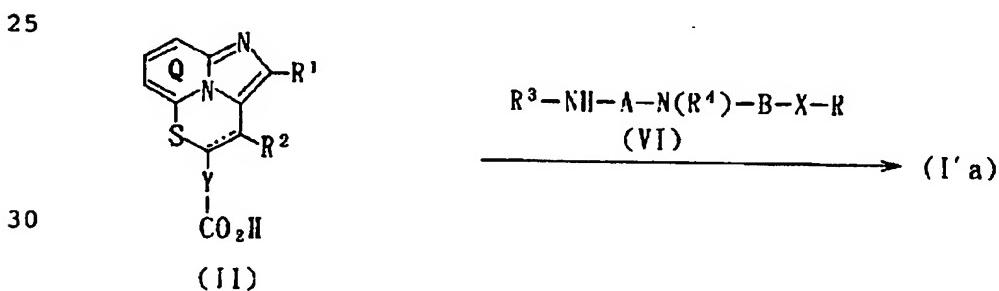
5 The compound (I') of the present invention can be synthesized by, for example, the following processes.

Process (A):



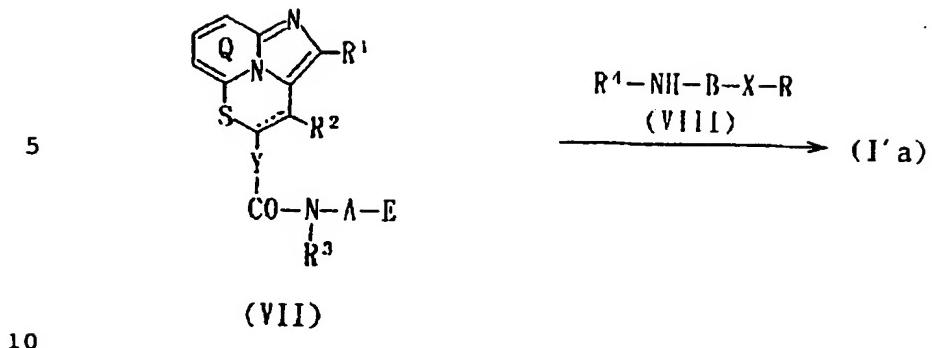
wherein E represents a leaving group such as, for example, halogen (e.g. chlorine, bromine, or iodine),
20 methanesulfonyloxy or p-toluenesulfonyloxy; and the other symbols are of the same meanings as defined hereinbefore.

Process (B): Z=CON(R³)



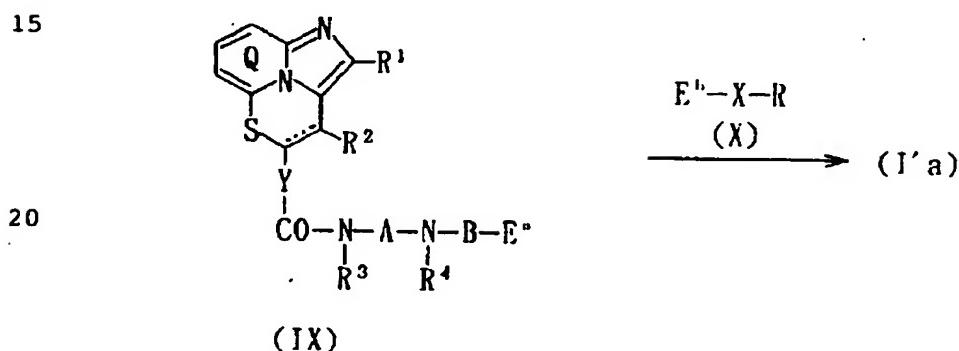
wherein all symbols are of the same meanings as defined hereinbefore.

35 Process (C): Z=CON(R³)



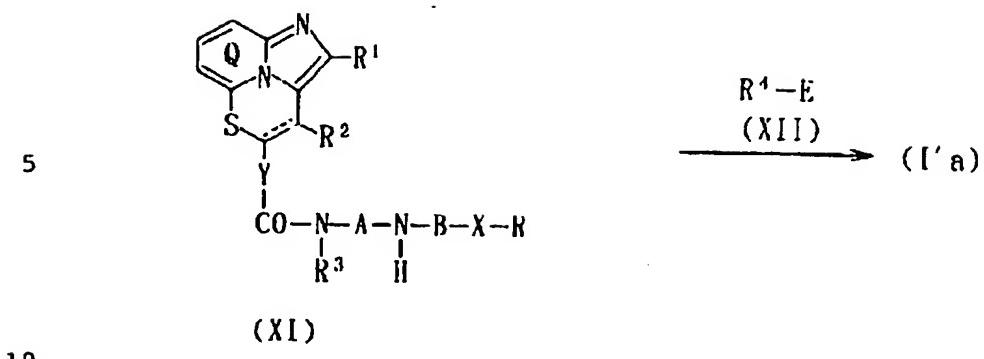
wherein all symbols are of the same meanings as defined hereinbefore.

Process D: Z=CON(R³)



25 wherein E^a and E^b independently represent a leaving group which leaves on reaction of E^a and E^b; thus, for example, when one represents hydrogen, the other represents halogen (e.g. chlorine, bromine, iodine), methanesulfonyloxy or p-toluenesulfonyloxy; and the
30 other symbols are of the same meanings as defined hereinbefore.

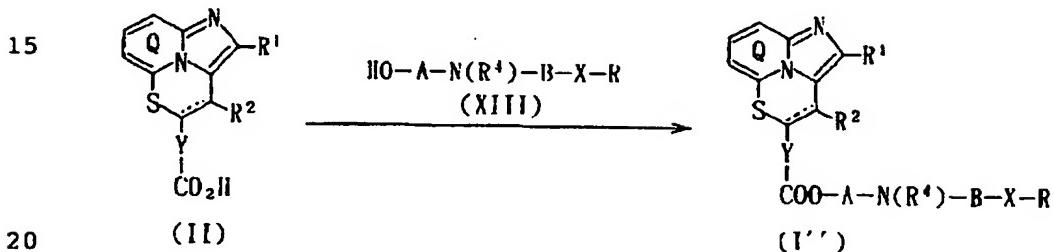
Process (E): $Z = \text{CON}(R^3)$



10

wherein all symbols are of the same meanings as defined hereinbefore.

Process (F): Z=COO



In the synthesis of the compound (I), the reaction between the compound (II') and compound: R²-CO-E¹ is carried out using one equivalent to a large excess, preferably 1 to 10 equivalents, of compound R²-CO-E¹ to one equivalent of the compound (II'). This reaction may be conducted in the presence of 1 to 10 equivalents of an inorganic base (e.g. potassium carbonate, sodium hydrogen carbonate, etc.) or an organic base (e.g. triethylamine, pyridine, dimethylaniline, 1,4-diazabicyclo[2.2.2]octane (DABCO), etc.). The reaction temperature may range from -30 to +100°C, preferably +25 to 80°C. The solvent which can be used in this reaction includes halogenated hydrocarbons (e.g. methylene chloride, chloroform, dichloroethane, etc.), ethers (e.g. diethyl ether, tetrahydrofuran,

etc.), esters (e.g. methyl acetate, ethyl acetate, etc.) and aprotic polar solvents (e.g. N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile, etc.). The reaction time may range from generally 10 minutes to 24 hours, and preferably 1 to 6 hours.

The cyclization reaction proceeds when the acyl compound is heated in the absence of a solvent at 100 to 150°C. This reaction can be carried out by using 1-10 equivalents of an inorganic salt (e.g. sodium hydride, lithium diisopropylamide, potassium carbonate, sodium hydrogen carbonate, etc.) or an organic base (e.g. 4-N,N-dimethylaminopyridine, triethylamine, pyridine, dimethylaniline, 1,4-diazabicyclo-[2.2.2]octane, etc.). The reaction temperature may range from 0 to 150°C. The solvent which can be used in this reaction includes halogenated hydrocarbons (e.g. methylene chloride, chloroform, dichloroethane, etc.), ethers (e.g. diethyl ether, tetrahydrofuran, etc.), esters (e.g. methyl acetate, ethyl acetate, etc.) and aprotic polar solvents (e.g. N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile, etc.). The reaction time may range from generally 10 minutes to 24 hours, and preferably 1 to 6 hours.

In the reduction of the double bond, one equivalent to a large excess, preferably 2 to 10 equivalents of a reducing agent are used. The reducing agent which can be used in this reaction includes metal hydride complex compounds (e.g. diisobutylaluminum hydride, sodium borohydride, sodium cyanoborohydride, lithium aluminum hydride, etc.) and diborane. The solvent which can be used in this reaction can be selected according to the type of reducing agent and includes alcohols (e.g. methanol, ethanol, etc.), ethers (e.g. tetrahydrofuran, dioxane, diethyl ether, etc.), halogenated hydrocarbons (e.g. methylene chloride, chloroform, etc.) and aprotic polar solvents

(e.g. N,N-dimethylformamide, dimethyl sulfoxide, etc.). The reaction time may range from 0.5 to 72 hours, preferably 1 to 24 hours. This reaction can be conducted at -80° to +100°C, preferably -80° to +30°C.

5 In the synthesis of the compound (I'), the reaction between the compound (V) and the compound (IV) according to Process (A) is carried out by using one equivalent to a large excess (1 to 10 equivalents) of the compound (IV) with respect to the compound (V).

10 This reaction may be conducted in the presence of 1 to 10 equivalents of a basic compound such as sodium hydroxide, potassium hydroxide, sodium hydride, potassium carbonate, triethylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]-7-undecene, or the like. This reaction can be carried out at -20 to +200°C. The solvent which can be used in this reaction includes lower alcohols (e.g. methanol, ethanol, propanol, etc.), ketones (e.g. acetone, methyl ethyl ketone, etc.), ethers (e.g. tetrahydrofuran etc.)

15 and aprotic polar solvents (e.g. N,N-dimethylformamide, dimethyl sulfoxide, etc.). Furthermore, this reaction can be conducted by using one equivalent to a large excess (1 to 10 equivalents) of sodium iodide as a reaction promotor. The reaction time may range from generally 10 minutes to 24 hours, and preferably 0.5 to 6 hours.

20 The dehydrative condensation reaction between compound (II) and the compound (VI) according to Process (B) can be conducted with advantage by the conventional amide-forming reaction procedure. This amide-forming reaction can be advantageously carried out by using an amide-forming reagent alone. The amide-forming reagent which can be used in this reaction includes 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, dicyclohexylcarbodiimide, 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide, meso-p-

toluenesulfonate, N,N'-carbonyldiimidazole,
diphenylphosphoramide, diethyl cyanophosphate and 1-
ethyl-3-(3-diethylaminopropyl)carbodiimide
hydrochloride. The amide-forming reagent is used
5 generally in a proportion of 1 to 3 equivalents to each
equivalent of the compound (II). This condensation can
be carried out advantageously by adding either a phenol
compound (e.g. 2,4,5-trichlorophenol,
pentachlorophenol, pentafluorophenol, 2-nitrophenol, 4-
10 nitrophenol, etc.) or an N-hydroxy compound (e.g. N-
hydroxysuccinimide, 1-hydroxybenzotriazole, N-
hydroxypiperidine, N-hydroxy-5-norbornene-2,3-
dicarbodiimide, etc.) and dicyclohexylcarbodiimide, to
the compound (II) so as to prepare an active ester and,
15 then, reacting the compound (VI) with this active
ester. The proportion of said phenol or N-hydroxy
compound is generally 1 to 3 equivalents to each
equivalent of the compound (II). The proportion of
dicyclohexylcarbodiimide is generally 1 to 3
20 equivalents to each equivalent of the compound (II).
And, this amide-forming reaction can be carried out
advantageously by reacting the compound (II) with an
acid chloride (e.g. ethyl chlorocarbonate, isobutyl
chlorocarbonate, benzyl chlorocarbonate, etc.) so as to
25 convert a mixed acid anhydride and, then, reacting it
with the compound (VI). The reaction can also be
carried out with advantage by reacting the compound
(II) with an acyl chloride (e.g. oxalyl chloride or
thionyl chloride) so as to convert the acid chloride
30 and, then, reacting it with the compound (VI). The
proportion of the acyl chloride is generally 1 to 3
equivalents per equivalent of the compound (II). These
amide- and ester-forming reactions can be carried out
using generally 1 to 3 equivalents of the compound (VI)
35 per equivalent of the compound (II). Moreover, if
necessary, the reaction can be accelerated by adding an

organic base such as a tertiary amine (e.g. triethylamine, pyridine, dimethylpyridine, N-methylpiperidine, etc.). The proportion of such a reaction promotor is generally one equivalent to a 5 large excess (preferably 1 to 10 equivalents) per equivalent of the compound (II). The reaction is generally conducted in the temperature range of -30°C to +50°C. This reaction may be conducted in the absence of a solvent or in a solvent. The solvent 10 which can be used in this reaction is not limited according to kinds of the reactions and includes ether, toluene, benzene, chloroform, methylene chloride, dioxane and tetrahydrofuran, etc. The reaction time 15 may range from generally 10 minutes to 48 hours, and preferably 1 to 24 hours.

The reaction between the compound (VII) and compound (VIII) according to Process (C) can be conducted typically under the same conditions as the reaction between the compound (V) and the compound (IV) 20 according to Process (A).

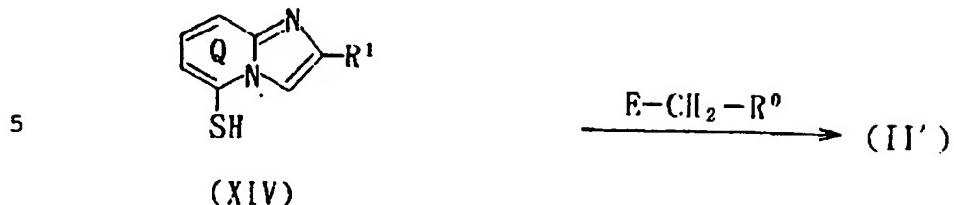
The reaction between the compound (IX) and the compound (X) according to Process (D) can be conducted typically under the same conditions as the reaction between the compound (V) and the compound (IV) 25 according to Process (A).

The reaction between the compound (XI) and the compound (XII) according to Process (E) can be conducted typically under the same conditions as the reaction between the compound (V) and the compound (IV) 30 according to Process (A).

The dehydrative condensation reaction between the compound (II) and the compound (XIII) according to Process (F) can be carried out typically under the same conditions as the reaction between the compound (II) 35 and the compound (VI) according to Process (B).

The compound (II') can be synthesized by, for

example, the following process.

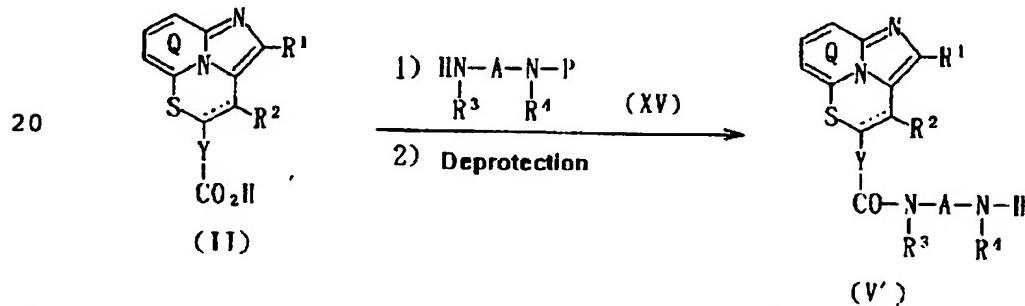


wherein all symbols are of the same meanings as defined hereinbefore.

10 The reaction between the compound (XIV) and compound: E-CH₂-R⁰ can be conducted typically under the same conditions as the reaction between the compound (V) and the compound (IV) according to Process (A).

15 The compound (V) can be synthesized by, for example, the following process.

i) Z=CON(R³):



25

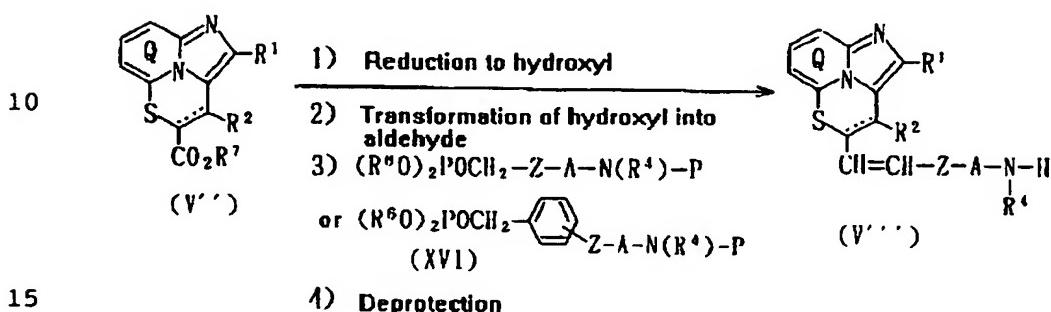
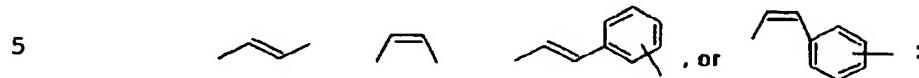
wherein P represents a hydrogen or an amino-protecting group; the other symbols are of the same meanings as defined hereinbefore.

30 The reaction between the compound (II) and the compound (XV) can be conducted typically under the same conditions as the reaction between the compound (VI) and the compound (V) according to Process (B). When P represents an amino-protecting group, the compound (V') can be obtained by removing the protective group

35 following the condensation reaction. Amino deprotection reactions are per se known reactions and

the relevant procedure can be selectively employed.

ii) Z represents CO, $-S(O)_n-$ ($n=0, 1, 2$) or $-SO_2N(R^3)-$ and Y represents



4) Deprotection

wherein R⁶ represents C₁₋₆ alkyl (e.g. methyl, ethyl, propyl, isopropyl, etc.), C₆₋₁₄ aryl (e.g. phenyl etc.) or C₇₋₁₆ aralkyl (e.g. benzyl etc.); R⁷ is of the same meaning as said protective group for the "optionally protected COOH group"; and the other symbols are of the same meanings as defined hereinbefore.

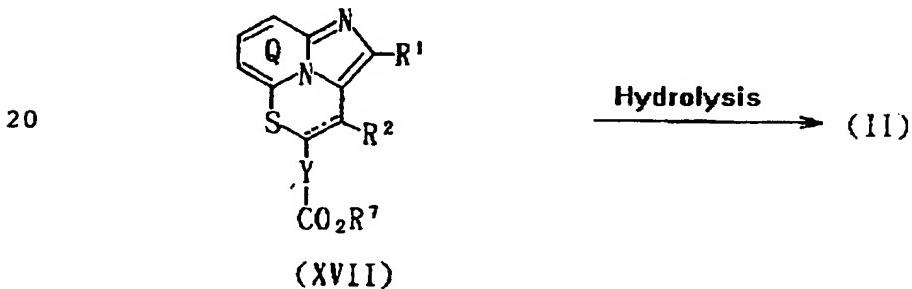
In the reduction of the compound (V"), a reducing agent is used in a proportion of one equivalent to a large excess, preferably 2 to 10 equivalents, relative to the compound (V"). The reducing agent which can be used in this reaction includes metal hydride complex compounds (e.g. diisobutylaluminum hydride, sodium borohydride, sodium cyanoborohydride, lithium aluminum hydride, etc.) and diborane. The solvent can be selected according to the kind of reducing agent used. Examples of the solvent are alcohols (e.g. methanol, ethanol, etc.), ethers (e.g. tetrahydrofuran, dioxane, diethyl ether, etc.), halogenated hydrocarbons (e.g. methylene chloride, chloroform, etc.) and aprotic polar solvents (e.g. N,N-dimethylformamide, dimethyl

sulfoxide, etc.). The reaction time may range from 0.5 to 72 hours, preferably 1 to 24 hours. This reaction can be conducted at -80 to +100°C, preferably -80 to +30°C. The oxidation of the resultant alcohol compound to the corresponding aldehyde compound can be carried out by, for example, using 1 to 20 equivalents of an oxidizing agent per equivalent of the alcohol compound. The oxidizing agent which can be used in the reaction includes active manganese dioxide, pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), dimethyl sulfoxide-acid anhydride (e.g. acetic anhydride, trifluoroacetic anhydride, etc.), dimethyl sulfoxide-thionyl chloride, dimethyl sulfoxide-sulfuryl chloride, dimethyl sulfoxide-oxalyl chloride, dimethyl sulfoxide-chlorine and dimethyl sulfoxide-dicyclohexylcarbodiimide (DCC) in the presence of an acid (e.g. phosphoric acid, trifluoroacetic acid, dichloroacetic acid, etc.). The solvent can be selected according to the oxidizing agent used, and includes ethers (e.g. tetrahydrofuran, dioxane, diethyl ether, etc.), halogenated hydrocarbons (e.g. methylene chloride, chloroform, etc.), ketones (e.g. acetone, methyl ethyl ketone, etc.), aprotic polar solvents (e.g. N,N-dimethylformamide, dimethyl sulfoxide, etc.), and so on. The reaction time may range from 0.5 to 48 hours, preferably 1 to 24 hours. The reaction temperature is selected according to the kind of oxidizing agent and may range from -80 to +100°C, preferably from -70 to +30°C.

The reaction between the aldehyde compound and the compound (XVI) can be generally conducted in a solvent with advantage. The solvent which can be used in this reaction includes halogenated hydrocarbons such as methylene chloride, chloroform, etc., ethers such as tetrahydrofuran, dimethoxyethane, dioxane, etc., aromatic hydrocarbons such as benzene, toluene, etc.,

alcohols such as methanol, ethanol, propanol, etc., amides such as N,N-dimethylformamide etc., aprotic polar solvents such as sulfoxides (e.g. dimethyl sulfoxide), mixtures of such solvents, and other solvents not adversely affecting this reaction. Generally, the compound (XVI) is preferably used in a proportion of 1 to 3 equivalents per equivalent of the aldehyde compound. A basic compound such as sodium hydride is used in a proportion of 1 to 10 equivalents, preferably 1 to 2 equivalents to the compound (XVI). The reaction temperature may range from 0°C to the boiling point of the solvent, preferably 0 to +80°C. The reaction time may range from about 0.5 to 24 hours, and preferably 0.5 to 10 hours.

The compound (II) can be synthesized by, for example, the following process.



25 wherein R' represents a carboxy-protecting group; and the other symbols are of the same meanings as defined hereinbefore.

30 The compound (III) can be produced in the same manner as the compound (II). Referring to the formulas (III) and (III-a), the compounds in which R' represents an optionally protected CH₂OH group or an optionally protected CHO group can be produced by subjecting the compounds in which R' represents carboxy to the per se known reduction reaction.

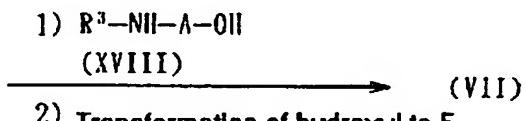
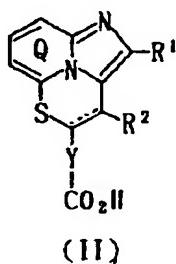
35 Hydrolysis of the compound (XVII) can be carried

out by treating the compound (XVII) with an acid or a base. Thus, the compound (XVII) is treated in a solution of an acid (e.g. hydrochloric acid, nitric acid, sulfuric acid, hydrobromic acid, iodic acid, etc.) or a base (e.g. sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide, etc.) in either water or a lower alcohol (e.g. methanol, ethanol, propanol, etc.) at 0 to +100°C, preferably +10 to 50°C, for 0.5 to 50 hours, preferably 1 to 5 hours.

10 The normality of the acid or base is preferably 1 to 10 N and more preferably 2 to 5 N.

The compound (VII) can be synthesized by, for example, the following process.

15



20

wherein all symbols are of the same meanings as defined hereinbefore.

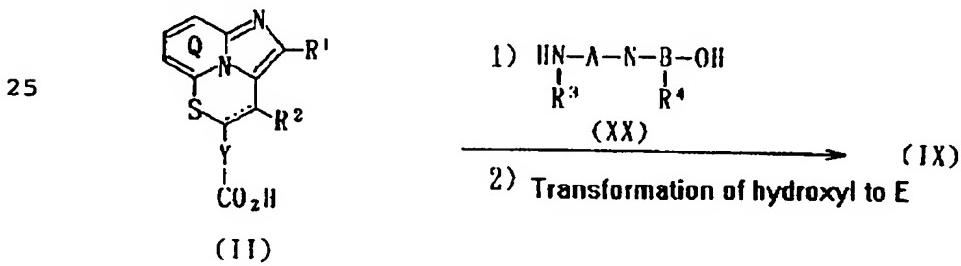
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The reaction between the compound (II) and the compound (XVIII) can be carried out typically under the same conditions as the reaction between the compound (II) and the compound (VI) according to Process (B). Transformation of hydroxyl to E, taking the case in which E represents halogen, is carried out using 1 to 10 equivalents, preferably 2 to 5 equivalents, of a halogenating agent such as a phosphorus halide (e.g. phosphorus trichloride, phosphorus oxychloride, phosphorus pentoxide, phosphorus trichloride, etc.), a red phosphorus-halogen or a thionyl chloride per equivalent of the alcohol compound. When E is

toluenesulfonyloxy or methanesulfonyloxy, 1 to 10 equivalents, preferably 2 to 5 equivalents, of toluene-sulfonyl chloride or methanesulfonyl chloride is reacted with one equivalent of the alcohol compound.

5 This reaction can be conducted in the presence of 1 to 10 equivalents of an inorganic base (e.g. potassium carbonate, sodium hydrogen carbonate, etc.) or an organic base (e.g. 4-N,N-dimethylaminopyridine, triethylamine, pyridine, dimethylaniline, 1,4-
10 diazabicyclo[2.2.2]octane (DABCO), etc.). The solvent which can be used in this reaction includes halogenated hydrocarbons (e.g. methylene chloride, chloroform, dichloroethane, etc.), ethers (e.g. diethyl ether, tetrahydrofuran, etc.), esters (e.g. methyl acetate, ethyl acetate, etc.) and aprotic polar solvents (e.g. N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile, etc.). This reaction temperature may range from 0 to +100°C, preferably 0 to +50°C. The reaction time may range from 10 minutes to 100 hours and preferably 3 to
15 20 hours.

The compound (IX) can be synthesized by, for example, the following process.

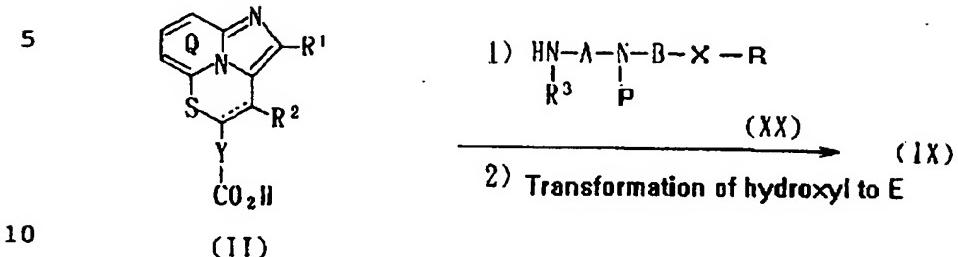


30 wherein all symbols are of the same meanings as defined hereinbefore.

The reaction for transformation of the compound (II) into the compound (IX) can be carried out
35 typically under the same conditions as the reaction for transformation of the compound (II) into the compound

(VII).

The compound (XI) can be synthesized by, for example, the following process.

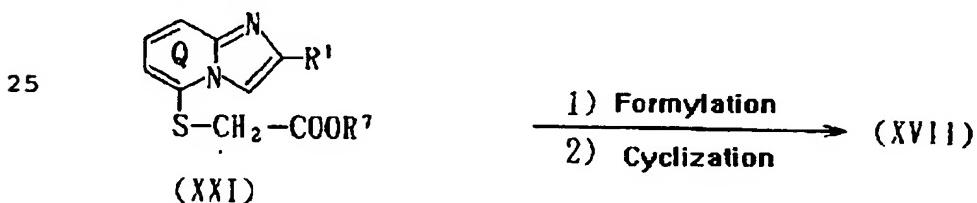


wherein all symbols are of the same meanings as defined hereinbefore.

The reaction for transformation of the compound
15 (II) into the compound (XI) can be carried out
typically under the same conditions as the reaction for
the transformation of the compound (II) into the
compound (V').

The compound (XVII) can be synthesized by, for example, the following process.

i) Where Y represents a bond and R² represents hydrogen:



30 wherein all symbols are of the same meanings as defined hereinbefore.

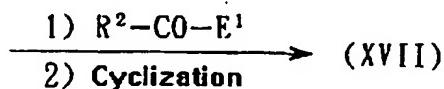
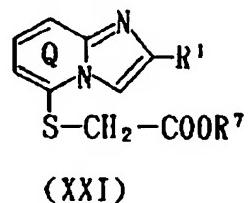
For the transformation of the compound (XXI) into the compound (XVII), a formylating agent is used in a proportion of 1 to 50 equivalents, preferably 1 to 10 equivalents, per equivalent of the compound (XXI). The formylating agent which can be used in this reaction

may, for example, be N,N-dimethylformamide-phosphorus oxychloride (Vilsmier reagent). In this process, the cyclization reaction can be caused to proceed under the formylating conditions. The solvent that can be used 5 includes ethers (e.g. tetrahydrofuran, dioxane, diethyl ether, etc.), halogenated hydrocarbons (e.g. methylene chloride, chloroform, etc.), hydrocarbons (e.g. hexane, pentane, benzene, toluene, etc.), aprotic polar solvents (e.g. N,N-dimethylformamide, dimethyl 10 sulfoxide, etc.), etc. The reaction time may range from 0.5 to 48 hours, preferably 1 to 24 hours. The reaction can be carried out at -20 to +150°C, preferably +80 to 120°C. The formylation of the compound (XXI) can also be carried out by reacting the 15 compound (XXI) with 1 to 3 equivalents of a base such as sodium hydride, potassium hydride, lithium diisopropylamide, and then reacting 1 to 10 equivalents, preferably 2 to 5 equivalents, of a formamide (e.g. N,N-dimethylformamide or N- 20 methylformanilide) or a formic acid ester (e.g. methyl formate or ethyl formate). The solvent which can be used in this formylation reaction includes ethers (e.g. tetrahydrofuran, dioxane, diethyl ether, etc.), hydrocarbons (e.g. hexane, pentane, benzene, toluene, 25 etc.) and aprotic polar solvents (e.g. N,N-dimethylformamide, dimethyl sulfoxide, etc.). The reaction time may range from 0.5 to 48 hours, preferably 1 to 24 hours. This reaction can be carried out at -100 to +50°C (preferably -80 to +30°C). The 30 compound (XVII) can be obtained by subjecting to ring closure reaction treating the formylation product with one equivalent to a large excess, preferably 1 to 50 equivalents, of an acid (e.g. acetic acid) at 0 to +150°C, preferably +80 to 130°C, for 1 to 24 hours, 35 preferably 10 to 20 hours. The solvent which can be used in this reaction includes carboxylic acids (e.g.

acetic acid, formic acid, etc.), ethers (e.g. tetrahydrofuran, dioxane, diethyl ether, etc.), hydrocarbons (e.g. hexane, pentane, benzene, toluene, etc.) and aprotic polar solvents (e.g. N,N-dimethylformamide, dimethyl sulfoxide, etc.).

5 ii) Where Y represents a bond and R² represents an optionally substituted hydrocarbon group:

10



15

wherein all symbols are of the same meanings as defined hereinbefore.

20

The reaction between the compound (XXI) and the compound: R²CO-E¹ is carried out using one equivalent to a large excess, preferably 1 to 10 equivalents, of the compound: R²CO-E¹ per equivalent of the compound

25

(XXI). This reaction may be conducted in the presence of 1 to 10 equivalents of an inorganic base (e.g. potassium carbonate, sodium hydrogen carbonate, etc.) or an organic base (e.g. triethylamine, pyridine, dimethylaniline, 1,4-diazabicyclo[2.2.2]octane (DABCO),

30

etc.). The reaction can be carried out at -30 to +100°C, preferably +25 to 80°C. The solvent which can be used in this reaction includes halogenated hydrocarbons (e.g. methylene chloride, chloroform, dichloroethane, etc.), ethers (e.g. diethyl ether, tetrahydrofuran, etc.), esters (e.g. methyl acetate, ethyl acetate, etc.) and aprotic polar solvents (e.g. N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile, etc.). The reaction time may range from 10 minutes to 24 hours, and preferably 1 to 6 hours. The

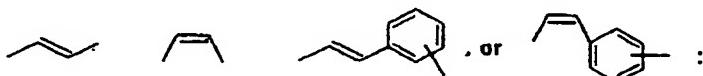
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ring closure reaction can be accelerated by heating the acyl compound in the absence of a solvent at +100 to

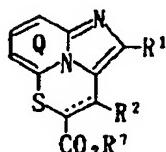
150°C. This reaction can be carried out using 1 to 10 equivalents of an inorganic salt (e.g. sodium hydride, lithium diisopropylamide, potassium carbonate, sodium hydrogen carbonate, etc.) or an organic base (e.g. 4-
 5 N,N-dimethylaminopyridine, triethylamine, pyridine, dimethylaniline, 1,4-diazabicyclo[2.2.2]octane, etc.). This reaction can be conducted at 0 to +150°C. The solvent which can be used in this reaction can be selected from halogenated hydrocarbons (e.g. methylene
 10 chloride, chloroform, dichloroethane, etc.), ethers (e.g. diethyl ether, tetrahydrofuran, etc.), esters (e.g. methyl acetate, ethyl acetate, etc.) and aprotic polar solvents (e.g. N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile, etc.). The reaction time may range from 10 minutes to 24 hours, and preferably 1 to
 15 6 hours.

iii) Where Y represents

20



25



1) Reduction to hydroxyl

2) Transformation of hydroxyl into aldehyde

3) Wittig reaction

(V')

(XVII)

30

wherein all symbols are of the same meanings as defined hereinbefore.

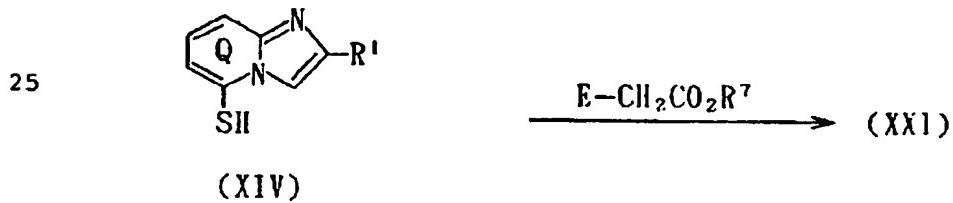
35

In the reduction of the compound (V'), a reducing agent is used in a proportion of one equivalent to a large excess, preferably 2 to 10 equivalents, relative to the compound (V'). The reducing agent which can be used in this reaction includes metal hydride complex compounds (e.g. diisobutylaluminum hydride, sodium borohydride, sodium cyanoborohydride, lithium aluminum

hydride, etc.) and diborane. The solvent which can be used in this reaction can be selected, according to the kind of reducing agent used, from among, for example, alcohols (e.g. methanol, ethanol, etc.), ethers (e.g. 5 tetrahydrofuran, dioxane, diethyl ether, etc.), halogenated hydrocarbons (e.g. methylene chloride, chloroform, etc.) and aprotic polar solvents (e.g. N,N-dimethylformamide, dimethyl sulfoxide, etc.), etc. The reaction time may range from 0.5 to 72 hours, 10 preferably 1 to 24 hours. This reaction can be carried out at -80 to +100°C, preferably -80 to +30°C. The oxidation of the resultant alcohol compound to the aldehyde compound can be carried out typically using 1 to 20 equivalents of an oxidizing agent per equivalent 15 of the alcohol compound. The oxidizing agent which can be used in this reaction includes active manganese dioxide, pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), dimethyl sulfoxide-acid anhydride (e.g. acetic anhydride, trifluoroacetic anhydride, 20 etc.), dimethyl sulfoxide-thionyl chloride, dimethyl sulfoxide-sulfuryl chloride, dimethyl sulfoxide-oxalyl chloride, dimethyl sulfoxide-chlorine and dimethyl sulfoxide-dicyclohexylcarbodiimide (DCC) in the presence of an acid (e.g. phosphoric acid, 25 trifluoroacetic acid, dichloroacetic acid, etc.). The solvent can be selected according to the oxidizing agent used, and includes ethers (e.g. tetrahydrofuran, dioxane, diethyl ether, etc.), halogenated hydrocarbons (e.g. methylene chloride, chloroform, etc.), ketones 30 (e.g. acetone, methyl ethyl ketone, etc.), aprotic polar solvents (e.g. N,N-dimethylformamide, dimethyl sulfoxide, etc.), etc. The reaction time may range from 0.5 to 48 hours, preferably 1 to 24 hours. The reaction temperature is selected according to the kind 35 of oxidizing agent and may range from -80 to +100°C, preferably -70 to +30°C.

The reaction of the aldehyde obtained as above with a Wittig reagent such as a phosphonium ylide or alkylidene-phosphorane is advantageously carried out in a solvent. The solvent which can be used in this reaction includes halogenated hydrocarbons methylene chloride, chloroform, etc.), ethers (e.g. tetrahydrofuran, dimethoxyethane, dioxane, etc.), aromatic hydrocarbons (e.g. benzene, toluene, etc., alcohols (e.g. methanol, ethanol, propanol, etc.), aprotic polar solvents (e.g. amides such as N,N-dimethylformamide, etc.), sulfoxides (e.g. dimethyl sulfoxide etc.), mixtures of said solvents, and other solvents not adversely affecting the reaction. The Wittig reagent is used generally in a proportion of 1 to 3 equivalents per equivalent of the aldehyde compound. This reaction is carried out in the temperature range of 0°C to the boiling point of the solvent, preferably 0 to 80°C. The reaction time may range from generally 1 to 24 hours, and preferably 0.5 to 10 hours.

The compound (XXI) can be synthesized by, for example, the following process.

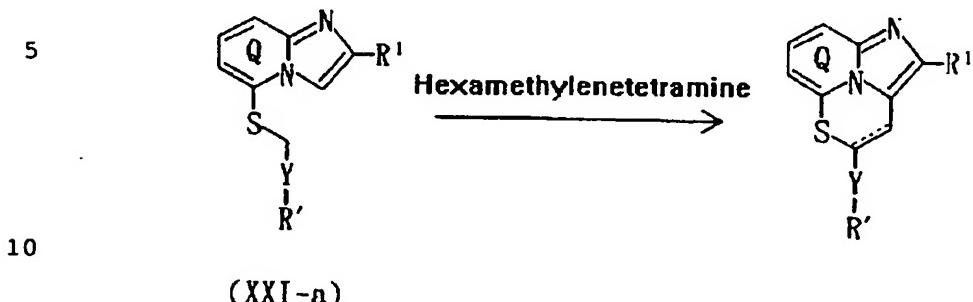


30 wherein the respective symbols are of the same meanings
as defined hereinbefore.

The reaction between the compound (XIV) and the compound: E-CH₂COOR' can be carried out typically under the same conditions as the reaction between the compound (V) and the compound (IV) according to Process (A).

The objective the compound (III-a) or a salt

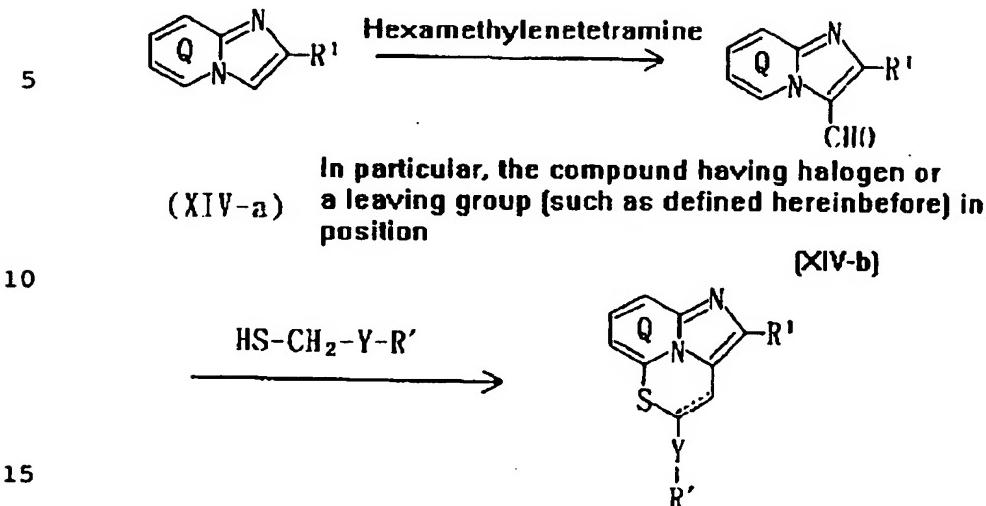
thereof, which is a useful production intermediate of the objective compound (I) or a salt thereof can be produced by, for example, the following process.



wherein all symbols are of the same meanings as defined hereinbefore.

In the above reaction, hexamethylenetetramine is used in a proportion of one equivalent to a large excess, preferably 1 to 10 equivalents, relative to the compound (XXI-a) or a salt thereof. The acid which can be used in this reaction includes an inorganic acid (e.g. hydrochloric acid, sulfuric acid, boric acid, etc.) or an organic acid (e.g. acetic acid, trifluoroacetic acid, formic acid, methanesulfonic acid, etc.). The preferable acid is acetic acid or boric acid. The acid is used in a proportion of one equivalent to a large excess, preferably 1 to 50 equivalents. The reaction temperature may range from about 0°C-200°C, preferably about 50°C to 150°C. The solvent which can be used in the reaction includes halogenated hydrocarbons (e.g. methylene chloride, chloroform, dichloroethane, etc.), ethers (e.g. diethyl ether, tetrahydrofuran, etc.), esters (e.g. methyl acetate, ethyl acetate, etc.), protic solvents (e.g. methanol, ethanol, etc.) and aprotic polar solvents (e.g. acetonitrile etc.). The solvent may contain water. Preferably, acetic acid which doubles as an acid and a solvent is used. The reaction time may

range from generally 10 minutes to 24 hours, and preferably 1 to 15 hours.



wherein all symbols are of the same meanings as defined hereinbefore.

In the above reaction, hexamethylenetetramine is used in a proportion of one equivalent to a large excess, preferably 1 to 10 equivalents, relative to the compound (XIV-a) or a salt thereof. As the acid, an inorganic acid (e.g. hydrochloric acid, sulfuric acid, boric acid, etc.) or an organic acid (e.g. acetic acid, trifluoroacetic acid, formic acid, methanesulfonic acid, etc.) is used. Preferred is acetic acid or boric acid. The proportion of the acid may range from one equivalent to a large excess, preferably 1 to 50 equivalents. The reaction temperature may range from about 0°C to 200°C, preferably about 50°C to 150°C. The solvent which can be used in this reaction includes halogenated hydrocarbons (e.g. methylene chloride, chloroform, dichloroethane, etc.), ethers (e.g. diethyl ether, tetrahydrofuran, etc.), esters (e.g. methyl acetate, ethyl acetate, etc.), protic solvents (e.g. methanol, ethanol, etc.), and aprotic polar solvents

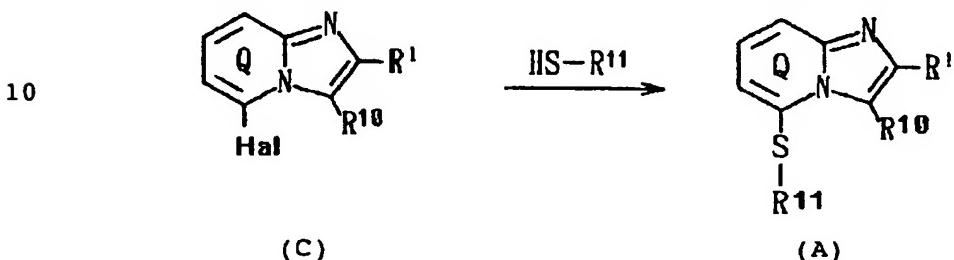
(e.g. acetonitrile etc.). The solvent may contain water. Preferably, acetic acid which doubles as an acid and a solvent is used. The reaction time may range from 10 minutes to 24 hours, and preferably 1 to 5 hours.

Then, with respect to the compound (XIV-b) or a salt thereof, a compound of the formula: HS-CH₂-Y-R' or a salt thereof (wherein all symbols of the same meanings as defined hereinbefore; preferably ethyl thioglycolate or the like) is reacted in a proportion of one equivalent to a large excess, preferably 1 to 10 equivalents. The base which can be used in this reaction may, for example, be an inorganic base (e.g. potassium carbonate, sodium carbonate, etc.), an organic base (e.g. triethylamine, pyridine, dimethylamine, 1,8-diazabicyclo[5.4.0]-7-undecene, etc.), an alcoholate (e.g. sodium methoxide, sodium ethoxide, potassium t-butoxide, etc.), an organometallic reagent (e.g. n-butyllithium etc.), sodium hydride, or sodium amide. The proportion of the base may range from one equivalent to a large excess, preferably 1 to 5 equivalents. The reaction temperature may range from about 0°C to 200°C, preferably about 25°C to 100°C. The solvent which can be used in this reaction includes halogenated hydrocarbons (e.g. methylene chloride, chloroform, dichloroethane, etc.), ethers (e.g. diethyl ether, tetrahydrofuran, etc.), esters (e.g. methyl acetate, ethyl acetate, etc.), protic solvents (e.g. acetic acid, methanol, ethanol, etc.), aprotic polar solvents (e.g. N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile, etc.). The reaction time may range from 10 minutes to 24 hours, and preferably 1 to 10 hours.

The compound (XXI-a) or a salt thereof can be produced in the same manner as the compound (XXI) or a salt thereof.

The compound (XIV-a) or a salt thereof can be produced by the per se known technology or in the same manner as the compound (XIV) or a salt thereof.

The compound represented by the formula (A), which
is a useful intermediate for producing the compound
(II) of this invention, or a salt thereof can be
produced by, for example, the methods described below.



wherein R¹⁰ is a hydrogen, an optionally substituted hydroxy group, an optionally substituted hydrocarbon group or an acyl group; Hal is a halogen atom; R¹¹ is an optionally substituted alkyl group; and the other symbols are of the same meanings as defined above. R¹⁰ is of the same meaning as the groups defined in R¹. R¹¹ is preferably a C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, etc.) which may be substituted by COOR¹⁵ (R¹⁵ is a lower alkyl group).

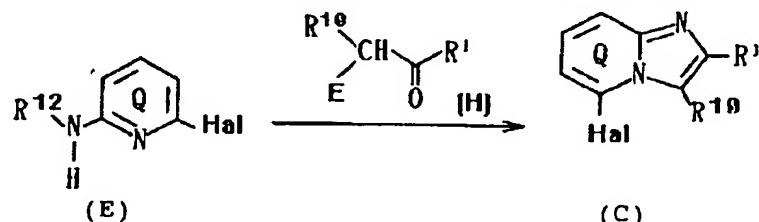
25 In the above-mentioned reaction for synthesizing
the compound (A) or a salt thereof, the compound
represented by the formula: HS-R¹¹ (R¹¹ is of the same
meaning as defined above), preferably, for example,
thioglycolic acid ethyl ester, is employed in an amount
30 of 1 to excess, preferably 1 to 5 equivalents, relative
to the compound (C) or a salt thereof. The reaction is
conducted in the presence or absence of a base,
preferably in the presence of a base. Examples of the
base include inorganic bases (e.g., potassium carbonate
35 and sodium carbonate), organic bases (e.g.,
triethylamine, pyridine, dimethylamine and 1,8-

diazabicyclo[5.4.0]-7-undecene), alcoholates (e.g., sodium methylate, sodium ethylate and tert-butoxy potassium), organometallic reagents (e.g., n-butyl lithium), sodium hydride and sodium amide. The amount 5 of the base in this reaction ranges from 1 to excess, preferably from 1 to 5 equivalents. The reaction temperature ranges from 0 to 100°C, preferably from 0 to 50°C. Examples of the solvent in this reaction include halogenated hydrocarbon (e.g., methylene 10 chloride, chloroform and dichloroethane), ethers (e.g., diethyl ether and tetrahydrofuran), esters (e.g., methyl acetate and ethyl acetate), aprotic solvents (e.g., N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile, acetone and toluene). The reaction time 15 ranges usually from 10 minutes to 24 hours, preferably from 1 to 10 hours.

The compound (C) or a salt thereof can be produced by reacting a compound (E) or a salt thereof with a compound (H) or a salt thereof, such as below.

20

25



wherein R¹² is a hydrogen or a protective group of amino; and the other symbols are of the same meanings as defined above.

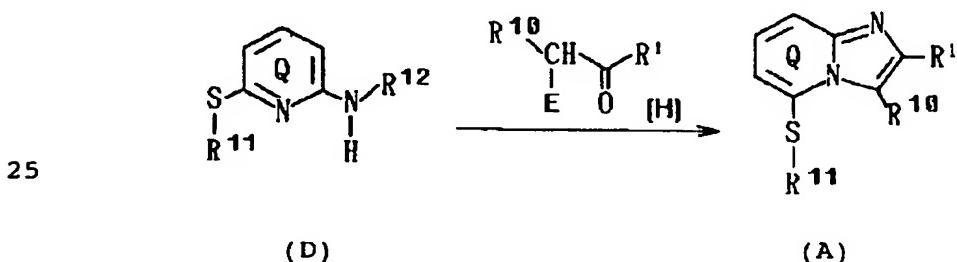
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In the above-mentioned reaction for synthesizing the compound (C) or a salt thereof, an α-keto derivative represented by the formula:



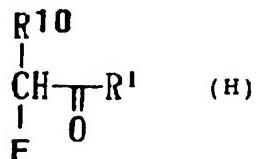
(wherein all symbols are of the same meaning as defined above), preferably chloroacetaldehyde, is employed in an amount of 1 to a large excess amount, preferably 1 to 5 equivalents, relative to the compound (E) or a salt thereof. The reaction temperature ranges from 0 to 150°C, preferably from 25 to 80°C. Examples of the solvent in this reaction include protonic solvents (e.g., water, methanol, ethanol and n-butanol) and aprotic solvents (e.g., N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile and acetone). The reaction time ranges usually from 10 minutes to 10 hours, preferably from 1 to 4 hours.

The compound (A) or a salt thereof can be produced by reacting a compound (D) or a salt thereof with a compound (H) or a salt thereof, such as below.



wherein all symbols are of the same meanings as defined above.

In the above-mentioned reaction, an α -keto derivative represented by the formula:

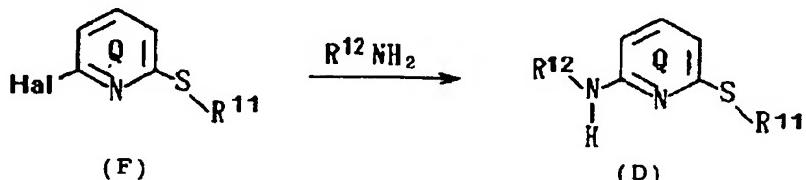


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10 temperature ranges from 0 to 150°C, preferably from 25 to 80°C. Examples of the solvent include protonic solvents (e.g., methanol, ethanol and n-butanol) and aprotic solvents (e.g., N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile and acetone). The reaction
15 time ranges from 10 minutes to 10 hours, preferably from 1 to 4 hours.

The compound (D) or a salt thereof can be produced by reacting the compound (F) or a salt thereof with $R^{12}NH_2$, such as the following reaction.

20



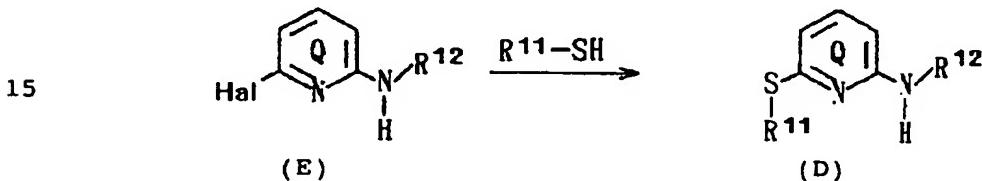
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wherein all symbols are of the same meanings as defined above.

In this reaction, 1 to a large excess amount of the compound represented by the formula: $R^{12}NH_2$, (wherein R² is of the same meaning as defined above), in an amount of 1 to a large excess, preferably from 1 to 10 equivalents, relative to the compound (F) of a salt thereof. Preferable examples of a compound: $R^{12}NH_2$, include ammonia and formamide. The reaction can be conducted in the absence or the presence of the solvent. Examples of the solvent in this reaction

include protonic solvents (e.g., water, methanol, ethanol and n-butanol) and aprotic solvents (e.g., N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile and acetone). The reaction temperature ranges from 1 to 5 250°C, preferably from 100 to 180°C. The pressure inside the reaction vessel ranges from normal to 40 kgcm⁻², preferably from normal to 20 kgcm⁻². The reaction time ranges from 10 minutes to 24 hours, preferably from 1 to 8 hours.

10 And, the compound (D) or a salt thereof can be produced by reacting a compound (E) or a salt thereof with a compound: $R^{11}-SH$, such as below.



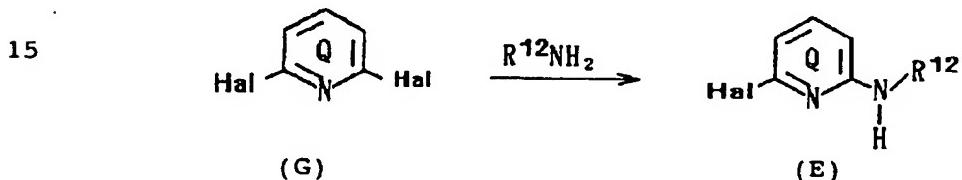
wherein all symbols are of the same meanings as defined above.

In this reaction, the compound represented by the formula: R¹¹-SH (wherein R¹¹ is of the same meaning as defined above, preferably, thioglycolic acid ethyl ester) is employed in an amount of 1 to excess, preferably from 1 to 5 equivalents, relative to the compound (E) or a salt thereof. The reaction is conducted in the presence or absence of a base.

Examples of the base to be employed include inorganic bases (e.g., potassium carbonate and sodium carbonate), organic bases (e.g., triethylamine, pyridine, dimethylamine and 1,8-diazabicyclo[5.4.0]-7-undecene), alcoholates (e.g., sodium methylate, sodium ethylate and tert-butoxy potassium), organometallic reagents (e.g., n-butyl lithium), sodium hydride and sodium amide. The amount of the base in this reaction ranges from 1 to excess, preferably from 1 to 5 equivalents.

The reaction temperature ranges from 0 to 100°C, preferably from 30 to 80°C. Examples of the solvent in this reaction include halogenated hydrocarbons (e.g., methylene chloride, chloroform and dichloroethane), ethers (e.g., diethyl ether and tetrahydrofuran), esters (e.g., methyl acetate and ethyl acetate), aprotic solvents (e.g., N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile, acetone and toluene). The reaction time ranges usually from 10 minutes to 24 hours, preferably from 1 to 10 hours.

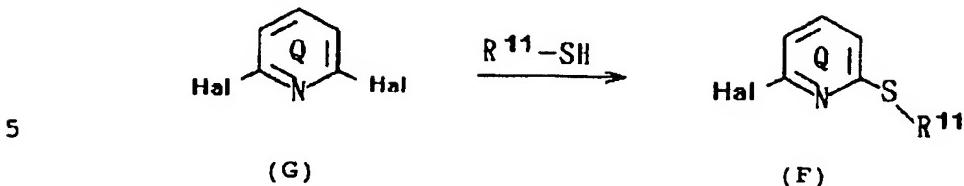
The compounds (E) and (F), or their salts can be produced from the compound (G) by the following reactions.



20 wherein all symbols are of the same meanings as defined above.

In this reaction, the compound: R¹²NH₂ (R¹² is of the same meanings as defined above, preferably ammonia and formamide) is employed in an amount ranging from 1 to a large excess, preferably from 1 to 10 equivalents, relative to the compound (G) or a salt thereof. The reaction is conducted in the absence or presence of a solvent. Examples of the solvent to be employed include protonic solvents (e.g., water, methanol, ethanol and n-butanol), aprotic solvents (e.g., N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile and acetone). The reaction temperature ranges from 1 to 250°C, preferably from 100 to 150°C. The pressure inside the reaction vessel ranges from normal to 50 kgcm⁻², preferably from normal to 20 kgcm⁻². The reaction time ranges from 10 minutes to 24 hours,

preferably from 1 to 8 hours.

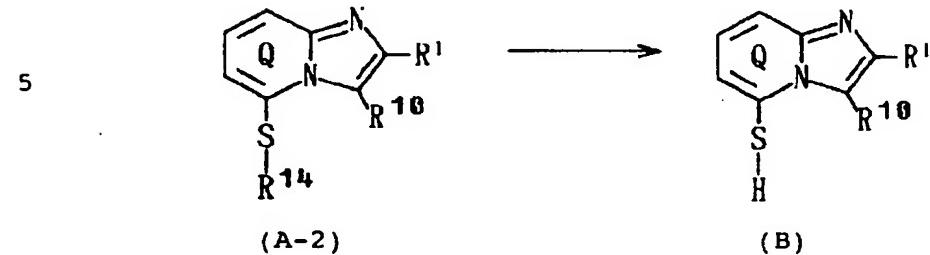


wherein all symbols are of the same meanings as defined above.

10 In this reaction, the compound: R¹¹-SH (wherein R⁴ is of the same meaning as defined above, preferably, e.g., thioglycolic acid ethyl ester) is employed in an amount of 1 to excess, preferably from 1 to 2 equivalents, relative to the compound (G) or a salt thereof. The reaction is conducted in the presence or absence of a base. Examples of the base to be employed include inorganic bases (e.g., potassium carbonate and sodium carbonate), organic bases (e.g., triethylamine, pyridine, dimethylamine and 1,8-diazabicyclo[5.4.0]-7-undecene), alcoholates (e.g., sodium methylate, sodium ethylate and tert-butoxy potassium), organometallic reagents (e.g., n-butyl lithium), sodium hydride and sodium amide. The amount of the base in this reaction ranges from 1 to excess, preferably from 1 to 2 equivalents. The reaction temperature ranges from 0 to 100°C, preferably from 0 to 50°C. Examples of the solvent in this reaction include halogenated hydrocarbons (e.g., methylene chloride, chloroform and dichloroethane), ethers (e.g., diethyl ether and tetrahydrofuran), esters (e.g., methyl acetate and ethyl acetate), aprotic solvents (e.g., N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile, acetone and toluene). The reaction time ranges usually from 10 minutes to 24 hours, preferably from 1 to 10 hours.

35 The compound (B) can be derived from a compound

(A-2) or a salt thereof which is the compound (A) in which R¹¹ is R¹⁴ (R¹⁴ is alkyl group), by dealkylation.



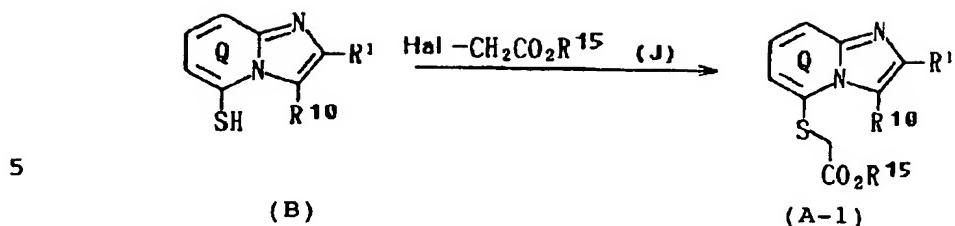
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wherein R¹⁴ is alkyl.

The "alkyl" of R¹⁴ includes C₁₋₆ alkyl such as methyl, ethyl, propyl.

In this reaction, a base is employed in an amount of 1 to large excess relative to the compound (A-2) or a salt thereof. Examples of the base to be employed include inorganic bases (e.g., potassium carbonate and sodium carbonate), organic bases (e.g., triethylamine, pyridine, dimethylamine and 1,8-diazabicyclo[5.4.0]-7-undecene), alcoholates (e.g., sodium methylate, sodium ethylate and tert-butoxy potassium), organometallic reagents (e.g., n-butyl lithium), sodium hydride and sodium amide, preferably sodium hydride, n-butyl lithium, tert-butoxy potassium and sodium amide. The reaction temperature ranges from 50 to 200°C, preferably from 100 to 180°C. Examples of the solvent in this reaction include halogenated hydrocarbons (e.g., chloroform and dichloroethane), ethers (e.g., tetrahydrofuran), esters (e.g., ethyl acetate), aprotic solvents (e.g., N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile, toluene and xylene). The reaction time ranges usually from 10 minutes to 10 hours, preferably from 1 to 3 hours.

35 Additionally stating, the compound (II) can be converted, by for example the method shown below, to the compound (I-1) included in the compound (I).



wherein R¹⁵ is a lower alkyl group such as methyl, ethyl; and other symbols are of the same meanings as defined above.

One equivalent to a large excess (1 to 10 equivalents) of the compound: Hal-CH₂COOR¹⁵ is employed relative to the compound (B), or a salt thereof. And, 1 to 10 equivalents of a basic compound such as sodium hydroxide, potassium hydroxide, sodium hydride, potassium carbonate, triethylamine, diisopropyl ethylamine and 1,8-diazabicyclo[5.4.0]-7-undecene may optionally be employed. The reaction can be conducted at temperatures ranging from -20 to +200°C. Examples of the solvent in this reaction include water, lower alcohols (e.g., methanol, ethanol and propanol), ketones (e.g., acetone and methyl ethyl ketone), ethers (e.g., tetrahydrofuran) and aprotic solvents (e.g., N,N-dimethylformamide and dimethyl sulfoxide). For this reaction, one equivalent to a large excess amount (1 to 10 equivalents) of sodium iodide can be optionally added as an accelerating agent of this reaction. The reaction time ranges usually from 10 minutes to 24 hours, preferably from 0.5 to 6 hours.

30 In the above reactions according to the present invention and the reactions for synthesizing the starting compounds used there, where any starting material compound has an amino group, a carboxyl group and/or a hydroxyl group as a substituent, such
35 functional group or groups may be previously blocked or masked using protective groups which are conventionally

used in peptide chemistry and the objective compound can then be obtained by eliminating the protective group or groups after the intended reaction.

The protective group that can be used for the amino function includes C₁₋₆ alkyl-carbonyl (e.g. formyl, methylcarbonyl, ethylcarbonyl, etc.), phenylcarbonyl, C₁₋₆ alkyl oxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, etc.), phenyloxycarbonyl (e.g. benzoxy carbonyl etc.), C₇₋₁₀ aralkyl(oxy)carbonyl (e.g. benzyloxycarbonyl etc.), trityl, phthaloyl, etc., each of which may be substituted. The substituent group includes halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), C₁₋₆ alkyl-carbonyl (e.g. methylcarbonyl, ethylcarbonyl, butylcarbonyl, etc.), nitro, etc. The number of substituents may range from 1 to about 3.

The protective group that can be used for the carboxyl function includes C₁₋₆ alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), phenyl, trityl, silyl, etc., each of which may be substituted. The substituent group includes halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), C₁₋₆ alkyl-carbonyl (e.g. formyl, methylcarbonyl, ethylcarbonyl, butylcarbonyl, etc.), nitro, etc. The number of substituents may range from 1 to about 3.

The protective group that can be used for the hydroxyl function includes C₁₋₆ alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), phenyl, C₇₋₁₀ aralkyl (e.g. benzyl etc.), C₁₋₆ alkyl-carbonyl (e.g. formyl, methylcarbonyl, ethylcarbonyl, etc.), phenyloxycarbonyl, C₇₋₁₀-aralkyloxy-carbonyl (e.g. benzyloxycarbonyl etc.), pyranyl, furanyl, silyl, etc., each of which may be substituted. The substituent group present includes halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), C₁₋₆ alkyl,

phenyl, C₇₋₁₀ aralkyl, nitro, etc. The number of substituents may range from 1 to about 4.

Removal of such protective groups can be carried out by techniques either known per se or analogous to known techniques. By way of illustration, a method using an acid or a base, reductive deprotection, and a technique using any of ultraviolet light, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate, etc. 10 can be mentioned.

The compound (I) obtained by any of the above processes can be isolated and purified by the conventional procedures such as recrystallization, distillation, chromatography, etc. When the thus-15 obtained compound (I) is the free compound, it can be converted to a salt by a per se known procedure or an analogous procedure (e.g. neutralization). Conversely when the product compound is a salt, it can be converted to either the free compound or a different 20 salt by the per se known procedure or an analogous procedure.

Furthermore, when the compound (I) is an optically active compound, it can be fractionated into the S- and R-compounds by the conventional optical resolution 25 technology.

The starting compounds for the compound (I) or salt of the present invention may be salts and the kind of salt is not critical only if the reaction involved proceeds successfully. For example, the kinds of salts 30 mentioned for the compound (I) can be used.

The compound (I) and its salt of the present invention have an excellent LDL receptor up-regulating lipids-lowering and blood sugar-lowering activity, and are low toxicity. Therefore, the compound (I) or a 35 salt thereof can be safely used in mammals (e.g. mouse, rat, hamster, rabbit, cat, dog, bovine, horse, sheep,

monkey, man, etc.) as a prophylactic and therapeutic agent for atherosclerotic diseases, hyperlipemia (hyperlipidemia), diabetes and diabetic complications.

5 The compound (I) or its salt can be administered either in the bulk form or in the form of a pharmaceutical composition. The pharmaceutical composition can be provided by the established pharmaceutical procedure using conventional carriers
10 and additives selected from among, for example, an excipient (e.g. calcium carbonate, kaolin, sodium hydrogen carbonate, lactose, starch, crystalline cellulose, talc, granulated sugar, porous substances, etc.), a binder (e.g. dextrin, gum, starch alcohol,
15 gelatin, hydroxypropylcellulose, hydroxypropylmethylcellulose, pullulan, etc.), a disintegrator (e.g. carboxymethylcellulose calcium, croscarmellose sodium, crospovidone, low-substitution-degree hydroxypropylcellulose, partially dextrinized starch, etc.), a
20 lubricant (e.g. magnesium stearate, calcium stearate, talc, starch, sodium benzoate, etc.), a coloring agent (e.g. tar color, caramels, iron sesquioxide, titanium oxide, riboflavins, etc.), a corrigent (e.g. sweeteners, perfumes, etc.), a stabilizer (e.g. sodium sulfite etc.), a preservative (e.g. parabens, sorbic acid, etc.), in suitable proportions. The prophylactic and therapeutic agent or composition of the present invention should contain a therapeutically or prophylactically effective amount of the compound (I)
25 or a salt thereof. The proportion of the compound (I) or salt in the total composition is generally 0.1 to 100 weight %. The pharmaceutical composition of the invention may contain one or more other medicinally active substances in addition to the compound (I) or
30 salt thereof and there is no limitation on the kinds of active substances which can be used only if the object
35

of the invention can be accomplished. Thus, such active substances can be formulated in suitable amounts. The specific dosage form which can be used includes tablets (inclusive of sugar-coated tablets and 5 film-coated tablets), pills, capsules, granules, fine granules, powders, syrups, emulsions, suspensions, injections, inhalants, ointments. Such dosage forms can be respectively manufactured by the known pharmaceutical procedures (such as the procedures 10 directed in the Japanese Pharmacopoeia).

Specifically, tablets can be prepared by granulating the compound (I) or a salt thereof as it is, or granulating a homogeneous mixture of it with an excipient, binder, disintegrator or other appropriate 15 additives according to a suitable method, then adding a lubricant, etc., and compressing the mixture for shaping. Alternatively, tablets can directly be prepared by compressing the compound (I) or a salt thereof as it is or a homogeneous mixture of it with an excipient, binder, disintegrator or other appropriate 20 additives. Furthermore, tablets can also be prepared by compressing granules per se prepared in advance or a homogeneous mixture of it with an appropriate additive. If necessary, the composition may contain a colorant, 25 corrigent, etc. Further, the composition may be coated with an appropriate coating agent. Injections can be prepared by charging a suitable amount of the compound (I) or a salt thereof into water for injection, physiological saline, Ringer's solution in the case of 30 using an aqueous solvent, or into vegetable oils in the case of using a nonaqueous solvent to make a suitable amount of the suspension or emulsion of it, and also by sealing a suitable amount of the compound (I) or a salt thereof into vials for injection.

35 Examples of the carriers for oral composition include materials conventionally used in pharmaceutics

such as starch, mannit, crystalline cellulose, carboxymethylcellulose, etc. Examples of the carriers for injections include distilled water, physiological saline, glucose solution, transfusion solution, etc.

- 5 In addition, additives generally used in pharmaceutics can appropriately be added.

The pharmaceutical composition of the present invention is of value as a drug because of its low toxicological potential and excellent LDL receptor up-regulating, lipids-lowering and blood sugar-lowering actions. Thus, the composition of the invention is useful for the prophylaxis and therapy of diseases caused by said pharmacological properties. Specifically, the composition can be used in the treatment or prevention of atherosclerosis, hyperlipemia, diabetes, diabetic complications, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, arrhythmia, peripheral vascular disease, thrombosis, disorders of pancreas, sequelae of myocardial infarction, valvular disease of the heart, and other diseases.

The compound (I) and its salt have cholesterol and triglyceride lowering activities. These biological properties suggest that the compound (I) and its salt are particularly suited for the therapy and prophylaxis of hyperlipemia (particularly hypertriglyceridemia, hyperlipoproteinemia, hypercholesterolemia) and the associated atherosclerotic vascular lesions and secondary diseases (e.g. coronary artery disease, ischemic diseases of the brain, aneurysm, cerebral arteriosclerosis, peripheral arteriosclerosis, intermittent claudication, gangrene).

In the treatment of these diseases, the compound (I) or salt of the invention can be used prophylactically and/or therapeutically, either independently or in combination with other lipids-

lowering or cholesterol lowering agents. In such cases, the active substances are preferably administered in an oral dosage form, and, if necessary, they can be administered rectally in the suppository form. The active substances which can be used in multiple-drug regimens include (1) fibrates (e.g. clofibrate, bezafibrate, gemfibrozil, etc.), nicotinic acid and its derivatives and analogs (e.g. acipimox, probucol, etc.), (2) bile salt binding resins (e.g. colestyramin, colestipol, etc.), cholesterol absorption inhibitors (e.g. sitosterol, neomycin, etc.), (3) cholesterol biosynthesis inhibitors (e.g. HMG-CoA reductase inhibitors such as lovastatin, simvastatin, pravastatin, etc.), and squalene epoxidase inhibitors (e.g. NB-598 and its analogs, etc.).

Among other active substances which can be used in combination with the compound (I) or salt are squalene-lanosterol cyclases (e.g. decalin derivatives, azadecalin derivatives, indan derivatives, etc.).

Furthermore, because the compound (I) and its salt have lipids-lowering activity and blood sugar-lowering activity in diabetic fatty rats, they are expected to ameliorate insulin resistance. In consideration of these biological properties, the compound (I) and its salt are particularly suited for the treatment or prevention of hyperglycemia and its secondary diseases such as diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, diabetic vascular diseases, etc. or insulin resistance and its associated diseases such as hypertension and impaired glucose tolerance, and even such secondary diseases as diseases of the heart, ischemic diseases of the brain, intermittent claudication, gangrene, etc.

In the prophylaxis and treatment of those diseases, the compound (I) or a salt thereof can be independently used or in combination with other

hypoglycemic agents or antihypertensive agents. In such applications, these compounds are preferably administered in oral dosage forms and, in certain cases, may be administered rectally in the suppository form. The active substances that can be used in combination include (1) insulin preparations (e.g. human insulin etc.), (2) sulfonylureas (e.g. glibenclamide, glyclazide, etc.), (3) α -glucosidase inhibitors (e.g. vogribose, acarbose, etc.), (4) insulin sensitizers (e.g pioglitazone, troglitazone, etc.), (5) aldose reductase inhibitors (e.g. epalrestat, tolrestat, etc.), and glycosylation inhibitors (e.g. aminoguanidine etc.).

It is also possible to use the compound (I) or salt of the invention in combination with known antihypertensive agents such as (1) diuretics (e.g. furosemide, spironolactone, etc.), (2) sympatholytics (e.g. atenolol etc.), (3) angiotensin II receptor antagonists (e.g. losartan, candesartan, etc.), (4) angiotensin I converting enzyme inhibitors (e.g. enalapril maleate, delapril hydrochloride, etc.), and (5) calcium channel blockers (e.g. nifedipine, manidipine hydrochloride, etc.).

The compound (I) or salt of the invention is suitable for the prophylaxis and therapy of diseases associated with hyperchylomicronemia such as acute pancreatitis. As the mechanism of onset of pancreatitis, it has been suggested that microthrombus are formed in pancreatic capillaries due to chylomicrons, or because of hyperchylomicronemia, the triglycerides decomposed by pancreatic lipase increase free fatty acids which stimulate the locus strongly. Therefore, as lowering as the compound (I) or salt of the invention has triglyceride lowering activity, it can be independently used alone or in combination with known therapies in the prevention and treatment of

pancreatitis. For the prophylaxis and therapy of this disease, the compound (I) or a salt thereof can be administered orally or topically, either independently or in combination with known active compounds such as
5 aprotinin, gabaxate methanesulfonate, nafamstat methanesulfonate, citicoline, urinastatin, etc.

Another noteworthy indication for the compound (I) or a salt thereof is secondary hyperlipidemia. It includes diabetes, insulin resistance (syndrome X),
10 hypopituitarism, nephrotic syndrome and chronic renal failure. While hyperlipidemia results from these diseases, it is generally acknowledged that in many cases hyperlipidemia exacerbate these diseases, thus forming a vicious cycle. In view of its lipid lowering activity, the compound (I) and its salt are suitable for the treatment and prevention of progression of such diseases. In this indication, the compound (I) or a salt thereof can be independently administered or in combination with known active compounds (e.g. dried
15 thyroid, levothyroxine sodium, liothyronine sodium, etc.), or in combination with prednisolone, methylprednisolone succinate sodium, furosemide, bumetanide, azosemide, etc. in combination therapies with therapeutic drugs for kidney diseases. These
20 medications are preferably made by the oral route.
25

A further possible application of the compound (I) or salt of the present invention is suppression of thrombus formation. Blood triglyceride and coagulation factor VII levels are positively correlated with each other and blood coagulation is suppressed when the triglyceride level is low due to the diet rich in ω -3 fatty acids, suggesting that hypertriglyceridemia encourages thrombus formation. Moreover, since VLDL in patients with hyperlipidemia is known to increase
30 secretion of plasminogen activator inhibitor from the vascular endothelial cells more prominently than does
35

VLDL in patients with normolipidemia, it is thought that triglycerides may decrease fibrinogenolysis. Therefore, in view of its triglyceride-lowering activity, the compound (I) or a salt thereof is considered suitable for the prevention and treatment of thrombosis. In this application, the compound (I) or salt can be independently administered or in combination with known therapeutic drugs such as dipyridamole, dilazep hydrochloride, thrombolytics (e.g. heparin sodium, urokinase, etc.) and, or anti-thrombins (e.g. aspirin, sulfapyrazone, ticlopidine hydrochloride, cilostazol, etc.), preferably by the oral route.

The dosage of the pharmaceutical composition of the present invention is dependent on the route of administration, patient's clinical status, age and body weight, and other factors but when it is to be administered orally to an adult patient, for example as a therapeutic agent for arteriosclerosis, a hypoglycemic agent, or a therapeutic agent for diabetic complications, the recommended daily dosage in terms of the compound (I) or a salt thereof is 0.2 to 50 mg/kg, preferably 0.5 to 30 mg/kg, which dosage is to be administered in one to a few divided doses. The route of administration may be whichever of the oral route and a non-oral route.

BEST MODE FOR CARRYING OUT THE INVENTION

The experimental data demonstrating the pharmacologic effects of the compound (I) and its salt are as follows.

Experimental Example 1: Increase in LDL-binding to HepG2 cells

LDL-binding was measured according to the method of J.L.Goldstein. HepG2 cells were purchased from ATCC (American type culture collection) and seeded in 6-well plate with collagen coating (Sumitomo Bakelite), and

cultured in Eagle's minimum essential medium (MEM) containing 10%-fetal bovine serum at 37°C for 4 days. After washing cells were cultured with MEM containing 10%-LPDS in the presence of test compound at a 5 concentration of 10 µM for 20 hours. 25-Hydroxycholesterol was used as a negative control at a concentration of 2.3 µM. After washing with phosphate buffered saline cells were incubated with MEM containing 25 mM-HEPES and 1%-bovine serum albumin 10 (fatty acid free) in the presence of human [¹²⁵I]LDL (4 µg/ml) at 6°C for 2 hours. After washing cells bound [¹²⁵I]LDL was dissociated with dextran sulfate and the radioactivity was measured (total binding). [¹²⁵I]LDL 15 binding to cells was also measured in the presence of LDL (300 µg/ml) as a non-specific binding (NSB). Specific [¹²⁵I]LDL-binding was calculated by subtracting NSB from total binding and was normalized by protein content measured by the method of lowry. Data was expressed as percentage of the control.

20 The result was shown in Table 1.

Table 1

	Example No.	LDL binding (% of control)
5	1	202.6
	2	172.5
10	3	194.2
	9	247.4
15	10	169.3
	22	125.5
20	26	189.1
	27	167.6
25	28	193.7
	36	218.5
30	46	165.8
	52	183.1
35	67	162.0
	76	281.5
40	77	168.3
	80	248.3
	113	140.4
	117	136.8

Experimental Example 2: Cholesterol lowering activity
in Golden hamster

Male Golden Syrian hamsters (110-130 g) were maintained freely on water and a laboratory diet (CE-2, Clea Japan Inc., Tokyo). Test compound was given orally at a dose of 20 mg/kg/d once daily for 4 days. Blood was taken from orbital sinus and plasma total

cholesterol and triglyceride were measured an automatic analyzer (Hitachi 7070, Hitachi Ltd., Tokyo) using commercial kits (Wako Pure Chemical Industries, Osaka), and plasma HDL-cholesterol using a commercial kit
5 (Kyowa Medex Co., Ltd., Tokyo) before and after the treatment of compound. Non-HDL cholesterol was calculated by subtracting HDL-cholesterol from total cholesterol.

The results are shown in Table 2.

Table 2

Example No.	Non-HDL-C (% of control)	TG (% of control)
5		
1	68.6	78.4
2	65.1	102.2
10	69.5	91.3
9	62.3	67.0
15	61.0	70.8
22	58.8	62.3
26	66.4	82.0
20	73.9	83.9
28	62.9	61.3
25	68.1	73.9
32	76.6	76.5
33	77.1	85.6
30	72.2	74.7
34	61.9	74.7
35	62.7	62.6
46	69.6	72.4
58	74.0	71.2
40	62.0	67.9
68	58.5	74.3
45	47.9	71.2
74	73.5	67.9
76	74.0	58.1
50	Non-HDL-C (non-HDL-cholesterol): [total cholesterol]-[HDL-cholesterol] TG: triglyceride	

It is apparent from Table 2 that whereas blood total cholesterol (TC) was elevated gradually in the control group, the elevation of blood cholesterol was suppressed by about 15-30% in the test groups. Thus, 5 in the groups treated with compound (I) or salt of the invention, the non-HDL-cholesterol level was suppressed as compared with the control group. Because the compound (I) and its salt lower both the blood LDL- and VLDL-cholesterol levels, they are of value for the 10 treatment of cardiovascular diseases such as atherosclerosis and hyperlipemia.

Experimental Example 3: Lipid-lowering effect in Wistar fatty rats

Male Waistar fatty rats were maintained on free 15 access to normal diet (CE-2, Clea Japan) and water. Body weights were measured at 10 weeks of age and the blood was taken from the orbital sinus and determined for plasma total cholesterol (TC), triglyceride (TG), glucose, and HDL-cholesterol (HDL-C) with Wako Pure 20 Chemical and Kyowa Medex kits using an automatic analyzer (Hitachi 7070). Non-HDL-cholesterol (non-HDL-C) was calculated by subtracting HDL-cholesterol from total cholesterol.

The rats were divided into 2 groups ($n=6$) and 30 mg/kg/day of the test compound (Example 22) in 0.5% methylcellulose solution was administered by a stomach tube to one of the groups once daily for 2 weeks (test group). 0.5% Methylcellulose solution only was similarly administered to the other group (control 30 group). On day 14, body weights were measured again and the blood was taken from the orbital sinus and determined for plasma total cholesterol, HDL-cholesterol, triglyceride, and glucose in the same manner as before.

35 The results are presented in Table 3.

Table 3

	Non-HDL-C (mg/dl)	Glucose (mg/dl)	TG (mg/dl)
5 Control group	39.9±3.7	366.8±72.0	324.7±74.2
10 Test group (Example 22)	30.0±5.2**	268.2±81.9*	258.3±38.4*

15 Mean ± SD (n=6)

* Significant at P<0.05 as compared with the control group of Wistar fatty rats

** Significant at P<0.01 as compared with the control group of Wistar fatty rats

It is apparent from Table 3 that the compound of the invention lowered not only glucose but also lowered non-HDL-cholesterol and triglyceride in the plasma significantly. Therefore, the compound of the invention is useful for the prevention and treatment of, for example, hyperglycemia or atherosclerosis. Since the compound of the invention lowers glucose significantly, it is of use as a therapeutic drug for diabetes or diabetic complications.

The following examples and reference examples are intended to describe the present invention merely in further detail and should by no means be construed as defining the scope of the invention. In these reference examples and examples, the term "room temperature" means 0 to +30°C, the ratio of solvents indicated in the description of the purification procedure by silica gel column chromatography is by volume (v/v), and the symbols used in the description of NMR data have the following meanings.

- s : singlet
- d : doublet
- t : triplet
- quint : quintet
- m : multiplet
- br : broad

Hz : Hertz

CDCl₃ : deuteriated chloroform

CD₃OD : deuteriated methanol

DMSO-D₆: deuteriated dimethyl sulfoxide

Reference Example 1

Synthesis of N-[2-(1-(tert-butoxycarbonyl)piperidin-4-ylidene)ethyl]phthalimide

1) Synthesis of tert butyl 4-(2-hydroxyethylidene)-
5 piperidine-1-carboxylate

To a solution of 19.901 g (73.888 mM) of tert-butyl 4-(ethoxycarbonylmethylene)piperidine-1-carboxylate in 100 ml of toluene was added 123 ml (185 mM) of 1.5 M diisobutylaluminum hydride-toluene at -78°C and the mixture was stirred at -78°C for 1 hour. Then, methanol was added at -78°C and the mixture was stirred for 0.5 hour to decompose the excess diisobutylaluminum hydride. Then, water was added under ice-cooling and the mixture was stirred for 2 hours. The resulting precipitate was filtered off with the aid of celite and the celite was washed with ethyl acetate. The filtrate and washes were pooled and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1 to 1/1) to provide the title compound.

Colorless liquid. Yield 15.292 g (91%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.469 (9H, s), 1.735 (1H, br s), 2.174 (2H, s, 5.9 Hz), 2.260 (2H, t, 5.9 Hz), 25 3.383-3.462 (4H, m), 4.172 (2H, d, 7.0 Hz), 5.493 (1H, t, 7.0 Hz).

2) Synthesis of tert-butyl 4-(2-bromoethylidene)-
piperidine-1-carboxylate

To a solution of 15.292 g (67.277 mM) of tert-butyl 4-(2-hydroxyethylidene)piperidine-1-carboxylate and 24.5 g (74.0 mM) of carbon tetrabromide in 150 ml of acetonitrile was added 19.4 g (74.0 mM) of triphenylphosphine at -78°C. Then, at room temperature, the mixture was stirred for 2 hours. This reaction mixture was distilled under reduced pressure to remove the solvent. To the residue was added

diethyl ether, followed by stirring, and the resulting precipitate was filtered off and washed with diethyl ether. The filtrate and washes were pooled and the solvent was distilled under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 30/1 to 9/1) to provide the title compound.

5 Colorless liquid. Yield 11.283 g (58%)
10 $^1\text{H-NMR}$ (CDCl_3 , 200 MHz) δ : 1.471 (9H, s), 2.203 (2H, t, 6.0 Hz), 2.297 (2H, t, 5.7 Hz), 3.405-3.478 (4H, m), 4.007 (2H, d, 8.4 Hz), 5.621 (1H, t, 8.4 Hz).

15 3) Synthesis of N-[2-[1-(tert-butoxycarbonyl)piperidin-4-ylidene]ethyl]phthalimide

A solution of 5.775 g (19.900 mM) of tert-butyl 4-(2-bromoethylidene)piperidine-1-carboxylate and 4.05 g (21.9 mM) of potassium phthalimide in 100 ml of *N,N*-dimethylformamide was stirred at 100°C for 1 hour. This reaction mixture was poured in water and extracted with 3 portions of ethyl acetate. The pooled organic layer was dried over anhydrous magnesium sulfate (MgSO_4) and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 6/1 to 3/1) to provide the title compound.

20 25 Light-yellow solid. Yield 5.473 g (77%)
 $^1\text{H-NMR}$ (CDCl_3 , 200 MHz), δ : 1.469 (9H, s), 2.143 (2H, t, 5.2 Hz), 2.458 (2H, t, 5.6 Hz), 3.401 (2H, t, 5.9 Hz), 3.480 (2H, t, 5.7 Hz), 4.294 (2H, d, 7.4 Hz), 5.367 (1H, t, 7.3 Hz), 7.693-7.759 (2H, m), 7.801-7.885 (2H, m).

30 Reference Example 2
Synthesis of N-[2-[1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]ethyl]phthalimide
1) Synthesis of tert-butyl 4-(2-hydroxyethyl)-3,6-dihydro-2*H*-pyridine-1-carboxylate

35 To a suspension of 0.66 g (17.5 mM) of lithium

aluminum hydride in 100 ml of diethyl ether was added a solution of 4.719 g (17.521 mM) of tert-butyl 4-(ethoxycarbonylmethyl)-3,6-dihydro-2H-pyridine-1-carboxylate in 50 ml of tetrahydrofuran dropwise under ice-cooling and the mixture was stirred at room temperature for 1 hour. To this reaction mixture was added ethyl acetate with ice-cooling to decompose the excess lithium aluminum hydride. Then, water was added until a white precipitate had formed. The precipitate was filtered off with the aid of celite and the celite was washed with ethyl acetate. The filtrate and washes were pooled and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1 to 1/1) to provide the title compound.

Colorless liquid. Yield 3.259 g (82%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.467 (9H, s), 1.663 (1H, br s), 2.086 (2H, br s), 2.282 (2H, t, 6.0 Hz), 3.502 (2H, t, 5.7 Hz), 3.709 (2H, t, 6.4 Hz), 3.879 (2H, br s), 5.480 (1H, br s).

2) Synthesis of tert-butyl 4-(2-bromoethyl)-3,6-dihydro-2H-pyridine-1-carboxylate

The procedure of Reference Example 1-2) was generally followed to provide the title compound as light-yellow liquid.

¹H-NMR (CDCl₃, 200 MHz) δ: 1.469 (9H, s), 2.071 (2H, br s), 2.573 (2H, t, 7.3 Hz), 3.443 (2H, t, 7.3 Hz), 3.500 (2H, t, 5.8 Hz), 3.884 (2H, br s), 5.476 (1H, br s).

30 3) Synthesis of N-[2-[1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]ethyl]phthalimide

The procedure of Reference Example 1-3) was generally followed to provide the title compound as light-yellow liquid.

35 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.456 (9H, s), 2.152 (2H, br s), 2.376 (2H, t, 6.8 Hz), 3.475 (2H, t, 5.7 Hz),

3.757 (2H, s), 3.793 (2H, t, 7.0 Hz), 5.347 (1H, br s), 7.689-7.755 (2H, m), 7.796-7.895 (2H, m).

Reference Example 3

Synthesis of tert-butyl 4-amino-1-piperidinecarboxylate

5 1) Synthesis of N-(1-benzylpiperidin-4-yl)trifluoroacetamide

To a solution of 25.94 g (136.3 mM) of 4-amino-1-benzylpiperidine and 22.1 ml (27.3 mM) of pyridine in 250 ml of tetrahydrofuran was added a solution of 21.2
10 ml (43.9 mM) of trifluoroacetic anhydride in 100 ml of tetrahydrofuran dropwise under ice-cooling and the mixture was stirred at room temperature overnight. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted
15 with 3 portions of ethyl acetate. The pooled organic layer was dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1) and the purified solid was
20 rinsed with diethyl ether to provide the title compound.

White solid. Yield 39.23 g (100%)

¹H-NMR (CDCl₃, 200 MHz) δ: 2.045-2.330 (4H, m), 2.675-
2.804 (2H, m), 3.515-3.573 (2H, m), 3.987-4.074
25 (1H, m), 4.150 (2H, s), 7.371-7.479 (5H, m),
7.957-7.806 (1H, m).

2) Synthesis of tert-butyl 4-trifluoroacetamide-1-piperidinecarboxylate

Using 4 g of 10% palladium-on-carbon (50% hydrous)
30 as a catalyst, 11.431 g (39.927 mM) of N-(1-benzyl-piperidin-4-yl)trifluoroacetamide was hydrogenated in 100 ml of methanol at room temperature and atmospheric pressure until the starting compound had disappeared (i.e. for 2 hours). The catalyst in the reaction
35 mixture was filtered off with the aid of celite and washed with methanol. The filtrate and washes were

pooled and the solvent was distilled off under reduced pressure to provide crude N-(piperidin-4-yl)trifluoroacetamide. This crude product was not purified but used as it was in the next reaction. To a
5 solution of the crude N-(piperidin-4-yl)trifluoroacetamide and 6.68 ml (47.9 mM) of triethylamine in tetrahydrofuran (50 ml)-methanol (20 ml) was added 9.59 g (43.9 mM) of di-tert-butyl dicarbonate dropwise at room temperature and the
10 mixture was stirred at the prevailing temperature overnight. The solvent was then distilled off under reduced pressure and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1) to provide the title compound.

15 White solid. Yield 8.505 g (72%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.321-1.555 (2H, m), 1.456 (9H, s), 1.921-1.995 (2H, m), 2.786-2.923 (2H, m), 3.890-4.140 (3H, m), 6.528 (1H, br d, 7.0 Hz).

20 3) Synthesis of tert-butyl 4-amino-1-piperidinecarboxylate

A solution of 7.35 g (24.8 mM) of tert-butyl 4-trifluoroacetamido-1-piperidinecarboxylate and 5.71 g (41.3 mM) of potassium carbonate in 50 ml of methanol was stirred at 60°C for 8 hours. This reaction mixture
25 was poured in aqueous solution of sodium hydrogen carbonate and the mixture was saturated with sodium chloride and extracted with 10 portions of ethyl acetate. The pooled organic layer was dried over MgSO₄ and the solvent was distilled off under reduced pressure to recover the title compound as light-yellow liquid. This crude product was not purified but used as it was in the next reaction.

30 ¹H-NMR (CDCl₃, 200 MHz), δ: 1.076-1.358 (4H, m), 1.456 (9H, s), 1.725-1.822 (2H, m), 2.703-2.855 (3H, m), 3.993-4.077 (2H, m).

35 Reference Example 4

Synthesis of N-[2-[1-(tert-butoxycarbonyl)-2,5-dihydro-1H-pyrrol-3-yl]ethyl]phthalimide

1) Synthesis of tert-butyl 3-oxopyrrolidine-1-carboxylate

5 To a solution of 25.63 g (0.2942 M) of 3-pyrrolidinol in tetrahydrofuran (150 ml)-ethanol (50 ml) was added 70.6 g (0.324 M) of di-tert-butyl dicarbonate dropwise at room temperature and the mixture was stirred at room temperature for 1 hour.

10 The solvent was then distilled off under reduced pressure to provide crude t-butyl 3-hydroxypyrrolidine-1-carboxylate. To a solution of 56.0 g (0.441 M) of oxalyl chloride in 400 ml of tetrahydrofuran was added 62.6 ml (0.883 M) of dimethyl sulfoxide dropwise at -

15 78°C and the mixture was stirred for 5 minutes. Then, a solution of the above crude tert-butyl 3-hydroxypyrrolidine-1-carboxylate in 150 ml of tetrahydrofuran was added dropwise and the mixture was stirred at -78°C for 15 minutes. To this reaction

20 mixture was added 246 ml (1.77 M) of triethylamine, and after room temperature was reestablished, the mixture was poured in water and extracted with 3 portions of ethyl acetate. The pooled organic layer was dried over MgSO₄ and the solvent was distilled off under reduced

25 pressure. This crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 6/1 to 3/1) to provide the title compound.

Yellow liquid. Yield 50.44 g (93%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.487 (9H, s), 2.588 (2H, t, 7.9 Hz), 3.756 (2H, s), 3.777 (2H, t, 7.8 Hz).

30 2) Synthesis of tert-butyl 3-(ethoxycarbonylmethyl)-2,5-dihydropyrrrole-1-carboxylate

35 A suspension of 60% sodium hydride in liquid paraffin, 3.41 g (85.2 mM), was washed with 3 portions of hexane and suspended in 50 ml of toluene. To this suspension was added a solution of 33.8 g (151 mM) of

ethyl diethylphosphonoacetate in 50 ml of toluene dropwise under ice-cooling and the mixture was stirred at room temperature for 30 minutes. This mixture was added to a solution of 25.42 g (137.2 mM) of 1-(tert-butoxycarbonyl)pyrrolidin-3-one in 200 ml of toluene dropwise at room temperature and the mixture was stirred at room temperature for 1.5 hours. This reaction mixture was diluted with diethyl ether and washed with water and the aqueous layer was extracted with 2 portions of diethyl ether. The pooled organic layer was dried over MgSO₄ and the solvent was distilled off under reduced pressure. The resulting crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 6/1 to 3/1) to provide the title compound.

Yellow liquid. Yield 8.201 g (23%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.280 (3H, t, 7.1 Hz), 1.472 (9H, s), 3.146 (2H, s), 4.119-4.226 (6H, m), 5.613-5.651 (1H, m).

20 3) Synthesis of tert-butyl 3-(2-hydroxyethyl)-2,5-dihydropyrrole-1-carboxylate

To a suspension of 1.22 g (32.1 mM) of lithium aluminum hydride in 150 ml of tetrahydrofuran was added a solution of 8.201 g (32.122 mM) of tert-butyl 3-(ethoxycarbonylmethyl)-2,5-dihydropyrrole-1-carboxylate in 50 ml of tetrahydrofuran dropwise under ice-cooling and the mixture was stirred at room temperature for 1 hour. To this reaction mixture was added ethyl acetate with ice-cooling to decompose the excess lithium aluminum hydride, and water was added until a white precipitate had formed. The precipitate was filtered off with the aid of celite and the celite was washed with ethyl acetate. The filtrate and washes were pooled and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1 to

1/1) to provide the title compound.

Colorless liquid. Yield 4.826 g (70%)

5 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.473 (9H, s), 1.767 (1H, br s), 2.387 (2H, br t, 6.2 Hz), 3.769 (2H, t, 6.3 Hz), 4.083-4.139 (4H, m), 5.499-5.537 (1H, m).

4) Synthesis of N-[2-[1-(tert-butoxycarbonyl)-2,5-dihydro-1H-pyrrol-3-yl]ethyl]phthalimide

To a solution of 4.818 g (22.590 mM) of tert-butyl 3-(2-hydroxyethyl)-2,5-dihydropyrrole-1-carboxylate and 10 4.72 ml (33.9 mM) of triethylamine in 100 ml of diethyl ether was added 2.10 ml (27.1 mM) of methanesulfonyl chloride dropwise under ice-cooling and the mixture was stirred at 0°C for 0.5 hour. This reaction mixture was poured in aqueous solution of sodium hydrogen carbonate 15 and extracted with 3 portions of diethyl ether. The pooled organic layer was dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was dissolved in 100 ml of N,N-dimethylformamide, followed by addition of 4.60 g (24.8 mM) of potassium phthalimide, and the mixture was 20 stirred at 100°C for 5 hours. This reaction mixture was poured in water and stirred and the precipitate that formed was recovered by filtration, rinsed with water, and dried to provide the title compound.

25 Light-brown solid. Yield 5.522 g (71%)

1H-NMR (CDCl₃, 200 MHz) δ: 1.482 (9H, s), 2.498 (2H, t, 6.9 Hz), 3.848 (2H, t, 7.1 Hz), 4.075 (4H, s), 5.504 (1H, s), 7.702-7.744 (2H, m), 7.832-7.874 (2H, m).

30 Reference Example 5

Synthesis of 1-(3-phenylpropan-1-yl)piperidin-3-ylmethylamine dihydrochloride

1) Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-3-ylmethyl]phthalimide

35 To a solution of 10.07 g (87.43 mM) of 3-piperidinemethanol and 19.1 g (96.2 mM) of 1-bromo-3-

phenylpropane in 150 ml of acetonitrile was added 18.1 g (131 mM) of potassium carbonate and the mixture was stirred at room temperature for one day. This reaction mixture was poured in water and extracted with 3 portions of ethyl acetate. The pooled organic layer was dried over MgSO₄, and the solvent was distilled off under reduced pressure to provide crude 1-(3-phenylpropan-1-yl)piperidine-3-methanol. This crude product was not purified but used as it was in the next reaction. To a solution of this crude 1-(3-phenylpropan-1-yl)piperidine-3-methanol and 14.6 ml (105 mM) of triethylamine in 150 ml of tetrahydrofuran was added a solution of 11.0 g (96.2 mM) of methanesulfonyl chloride in 50 ml of tetrahydrofuran dropwise under ice-cooling and the mixture was further stirred at the prevailing temperature for 0.5 hour. This reaction mixture was poured in water and extracted with 3 portions of ethyl acetate. The pooled organic layer was dried over MgSO₄, and the solvent was distilled off under reduced pressure. The residue was dissolved in 500 ml of N,N-dimethylformamide, followed by addition of 17.8 g (96.2 mM) of potassium phthalimide, and the mixture was stirred at 100°C overnight. This reaction mixture was poured in water and extracted with 3 portions of ethyl acetate. The pooled organic layer was dried over MgSO₄, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1/1 to ethyl acetate) to provide the title compound.

Yellow liquid. Yield 25.905 g (82%)

¹H-NMR (CDCl₃, 200 MHz) δ: 0.954-1.123 (1H, m), 1.437-2.153 (8H, m), 2.336 (2H, t, 7.9 Hz), 2.595 (2H, t, 7.7 Hz), 2.752-2.807 (2H, m), 3.542 (1H, dd, 7.0 Hz, 13.6 Hz), 3.624 (1H, dd, 6.9 Hz, 13.7 Hz), 7.105-7.295 (5H, m), 7.666-7.769 (2H, m), 7.804-

7.871 (2H, m).

2) Synthesis of N-tert-butoxycarbonyl-[1-(3-phenylpropan-1-yl)piperidin-3-ylmethyl]amine

To a solution of 10.770 g (29.713 mM) of N-[1-(3-phenylpropan-1-yl)piperidin-3-ylmethyl]phthalimide in 50 ml of ethanol was added 1.44 ml (29.7 mM) of hydrazine monohydrate and the mixture was refluxed for 2 hours. After this reaction mixture was cooled to room temperature, 7.78 g (35.7 mM) of di-tert-butyl dicarbonate was added and the mixture was stirred at room temperature for 1 hour. This reaction mixture was poured in aqueous solution of sodium hydroxide and extracted with 3 portions of ethyl acetate. The pooled organic layer was dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1/1 to ethyl acetate) to provide the title compound.

Light-yellow liquid. Yield 8.914 g (90%)

¹H-NMR (CDCl₃, 200 MHz) δ: 0.846-1.117 (1H, m), 1.434 (9H, s), 1.568-1.960 (8H, m), 2.339 (2H, t, 7.5 Hz), 2.616 (2H, t, 7.9 Hz), 2.757-2.835 (2H, m), 3.009 (2H, br s), 4.607 (1H, br s), 7.133-7.318 (5H, m).

25 3) Synthesis of 1-(3-phenylpropan-1-yl)piperidin-3-ylmethyamine dihydrochloride

In 50 ml of methanol was dissolved 8.902 g of N-tert-butoxycarbonyl-[1-(3-phenylpropan-1-yl)piperidin-3-ylmethyl]amine, followed by addition of 10 ml of concentrated hydrochloric acid, and the mixture was stirred at room temperature for 3 hours. This reaction mixture was concentrated to provide the title compound.

Light-yellow foam. Yield 8.200 g (100%)

¹H-NMR (CD₃OD, 200 MHz) δ: 1.212-1.434 (1H, m), 1.785-2.438 (6H, m), 2.728 (2H, t, 7.6 Hz), 2.776-3.032 (4H, m), 3.153 (2H, t, 8.6 Hz), 3.538-3.690 (2H,

m), 7.161-7.347 (5H, m).

Reference Example 6

Synthesis of 1-(3-phenylpropan-1-yl)-4,4'-bipiperidine dihydrochloride

5 1) Synthesis of 1-tert-butoxycarbonyl-1'-(3-phenylpropan-1-yl)-4,4'-bipiperidine

To a solution of 10.98 g (45.52 mM) of 4,4'-bipiperidine and 9.06 g (45.5 mM) of 1-bromo-3-phenylpropane in 150 ml of ethanol was added 18.9 g (137 mM) of potassium carbonate and the mixture was stirred at room temperature for one day. This reaction mixture was filtered and the solvent was removed from the filtrate under reduced pressure. The residue was dissolved in 100 ml of tetrahydrofuran, and after 11.9 g (54.6 mM) of di-tert-butyl dicarbonate was added, the mixture was stirred at room temperature for 6 hours. This reaction mixture was poured in aqueous solution of sodium hydroxide and extracted with 3 portions of ethyl acetate. The pooled organic layer was dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1 to 1/1 ethyl acetate) to provide the title compound.

Yellow solid. Yield 3.597 g (20%)

25 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.009-1.381 (6H, m), 1.451 (9H, s), 1.628-1.683 (4H, m), 1.744-1.896 (4H, m), 2.333 (2H, t, 7.7 Hz), 2.575-2.689 (4H, m), 2.946 (2H, br d, 11.8 Hz), 4.064-4.169 (2H, m), 7.127-7.305 (5H, m).

30 2) Synthesis of 1-(3-phenylpropan-1-yl)-4,4'-bipiperidine dihydrochloride

In 20 ml of methanol was dissolved 3.425 g (8.860 mM) of 1-tert-butoxycarbonyl-1'-(3-phenylpropan-1-yl)-4,4'-bipiperidine, followed by addition of 5 ml of concentrated hydrochloric acid, and the mixture was stirred at room temperature for 6 hours. This reaction

mixture was concentrated and crystallized from methanol-diethyl ether to provide the title compound. Light-yellow solid. Yield 2.965 g (93%)
¹H-NMR (CD₃OD, 200 MHz) δ: 1.413-1.659 (6H, m), 1.945-5 2.170 (6H, m), 2.715 (2H, t, 7.5 Hz), 2.860-3.131 (6H, m), 3.413 (2H, br d, 12.6 Hz), 3.595 (2H, br d, 12.4 Hz), 7.157-7.335 (5H, m).

Reference Example 7

Synthesis of N-[2-(3-phenylpropan-1-yl)-2,3-dihydro-1H-10 isoindol-5-ylmethyl]phthalimide

1) Synthesis of (7,7-dimethyl-5,9-dihydro-6,8-dioxabenzocyclohepten-2-yl)methanol

To a suspension of 25.1 g (661 mM) of lithium aluminum hydride in 1300 ml of tetrahydrofuran was added 50.77 g (264.2 mM) of 1,3-dioxo-1,3-dihydroisobenzofuran-5-carboxylic acid (trimellitic anhydride) in small portions under ice-cooling and the mixture was stirred at room temperature for one day. To this reaction mixture was added ethyl acetate with ice-cooling to decompose the excess lithium aluminum hydride and water was added until a white precipitate had formed. The precipitate was filtered off with the aid of celite and the celite was washed with ethyl acetate and ethanol. The filtrate and washes were pooled and the solvent was distilled off under reduced pressure. The crude [2,4-bis(hydroxymethyl)-phenyl]methanol thus obtained was dissolved in 100 ml of N,N-dimethylformamide. Then, 100 ml of acetone, 70 ml of 2,2-dimethoxypropane, and 5 g of DL-10-camphorsulfonic acid were added and the mixture was stirred at room temperature overnight. This reaction mixture was diluted with aqueous solution of sodium hydroxide and extracted with 6 portions of ethyl acetate. The pooled organic solution was dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel

column chromatography (hexane/ethyl acetate = 3/1 to 1/1) to provide the title compound.

White solid. Yield 20.20 g (37%)

5 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.502 (6H, s), 1.654 (1H, br s), 4.630 (2H, s), 4.839 (4H, s), 7.044 (1H, d, 7.8 Hz), 7.063 (1H, s), 7.152 (1H, d, 7.8 Hz).

2) Synthesis of tert-butyl-(7,7-dimethyl-5,9-dihydro-6,8-dioxabenzocyclohepten-2-yl)methoxydiphenylsilane

To a solution of 3.227 g (15.495 mM) of (7,7-dimethyl-5,9-dihydro-6,8-dioxabenzocyclohepten-2-yl)-methanol and 1.27 g (18.6 mM) of imidazole in 20 ml of N,N-dimethylformamide was added 4.69 g (17.0 mM) of tert-butylchlorodiphenylsilane at room temperature and the mixture was stirred for 2 hours. This reaction 10 mixture was poured in water and extracted with 3 portions of diethyl ether. The pooled organic layer was dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 15 = 30/1) to provide the title compound.

Colorless liquid. Yield 6.504 g (94%)

20 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.079 (9H, s), 1.511 (6H, s), 4.720 (2H, s), 4.837 (2H, s), 4.853 (2H, s), 7.011 (1H, s), 7.031 (1H, d, 8.0 Hz), 7.157 (1H, d, 7.8 Hz), 7.326 (6H, m), 7.659-7.718 (4H, m).

25 3) Synthesis of [4-(tert-butyldiphenylsiloxyethyl)-2-hydroxymethylphenyl]methanol

To a solution of 6.175 g (13.825 mM) of tert-butyl-(7,7-dimethyl-5,9-dihydro-6,8-dioxabenzocyclohepten-2-yl)methoxydiphenylsilane in 30 50 ml of tetrahydrofuran-water (4:1) was added 2 ml of trifluoroacetic acid with ice-cooling and the mixture was stirred at room temperature for 4 hours. This reaction mixture was poured in aqueous solution of sodium hydrogen carbonate and extracted with 3 portions 35 of ethyl acetate. The pooled organic layer was dried

over MgSO₄ and the solvent was distilled off under reduced pressure to provide the title compound.

Colorless liquid. Yield 5.720 g (100%)

5 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.090 (9H, s), 2.973 (2H, br s), 4.663 (4H, s), 4.749 (2H, s), 7.257-7.459 (14H, m), 7.656-7.702 (4H, m).

4) Synthesis of 5-(tert-butyldiphenylsiloxyethyl)-2-(3-phenylpropan-1-yl)-2,3-dihydro-1H-isoindole

To a solution of 5.867 g (14.429 mM) of [4-(tert-10 butyldiphenylsiloxyethyl)-2-hydroxymethylphenyl]methanol and 12.6 ml (72.1 mM) of N,N-diisopropylethylamine in 100 ml of acetonitrile was added a solution of 3.47 g (30.3 mM) of methanesulfonyl chloride in 10 ml of acetonitrile dropwise with ice-15 cooling and the mixture was stirred at 0°C for 0.5 hour. To this reaction mixture was added 2.15 g (15.9 mM) of 3-phenylpropylamine and the mixture was stirred at 80°C overnight. The solvent was then distilled off under reduced pressure and the residue was diluted with 20 aqueous solution of sodium hydrogen carbonate and extracted with 3 portions of ethyl acetate. The pooled organic layer was dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 6/1 to 3/1) to provide the 25 title compound.

Brown liquid. Yield 3.710 g (51%)

1H-NMR (CDCl₃, 200 MHz) δ: 1.080 (9H, s), 1.845-1.995 (2H, m), 2.739 (2H, t, 7.7 Hz), 2.754 (2H, t, 7.3 30 Hz), 3.919 (4H, s), 4.747 (2H, s), 7.155-7.469 (14H, m), 7.668-7.727 (4H, m).

5) Synthesis of 2-(3-phenylpropan-1-yl)-2,3-dihydro-1H-isoindol-5-ylmethanol

To a solution of 3.699 g (7.316 mM) of 5-(tert-35 butyldiphenylsiloxyethyl)-2-(3-phenylpropan-1-yl)-2,3-dihydro-1H-isoindole in 50 ml of tetrahydrofuran was

added 8.78 ml (8.78 mM) of 1.0N-tetrabutylammonium fluoride-tetrahydrofuran at room temperature and the mixture was stirred for 1 hour. This reaction mixture was poured in aqueous solution of sodium hydrogen carbonate and extracted with 3 portions of ethyl acetate. The pooled organic layer was dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1/1 to 10 ethyl acetate) to provide the title compound.

Brown liquid. Yield 1.840 g (94%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.846-1.998 (2H, m), 2.414 (1H, br s), 2.720 (2H, t, 7.7 Hz), 2.736 (2H, t, 7.5 Hz), 3.854 (2H, s), 3.894 (2H, s), 4.597 (2H, s), 7.078 (1H, s), 7.123 (2H, s), 7.154-7.336 (5H, m).

6) Synthesis of N-[2-(3-phenylpropan-1-yl)-2,3-dihydro-1H-isoindol-5-ylmethyl]phthalimide

To a solution of 1.835 g (6.863 mM) of 2-(3-phenylpropan-1-yl)-2,3-dihydro-1H-isoindol-5-ylmethanol and 1.43 ml (10.3 mM) of triethylamine in 50 ml of tetrahydrofuran was added 0.64 ml (8.24 mM) of methanesulfonyl chloride dropwise with ice-cooling and the mixture was stirred at 0°C for 0.5 hour. This reaction mixture was poured in aqueous solution of sodium hydrogen carbonate and extracted with 3 portions of diethyl ether. The pooled organic layer was dried over MgSO₄ and the solvent was distilled off under reduced pressure. The crude 2-(3-phenylpropan-1-yl)-2,3-dihydro-1H-isoindol-5-ylmethyl methanesulfonate thus obtained was dissolved in 60 ml of N,N-dimethylformamide, followed by addition of 1.40 g (7.55 mM) of potassium phthalimide, and the mixture was stirred at 100°C for 4 hours. This reaction mixture was poured in aqueous solution of sodium hydrogen carbonate and extracted with 3 portions of ethyl

acetate. The pooled organic solution was dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/ethyl acetate = 3/1 to 5 2/1) to provide a mixture of the objective compound and phthalimide. This product was dissolved in ethyl acetate and the solution was washed serially with aqueous solution of sodium hydroxide and saturated aqueous solution of sodium chloride. It was then dried 10 over anhydrous sodium sulfate (Na₂SO₄) and the solvent was distilled off under reduced pressure to provide the title compound.

Yellow liquid. Yield 0.401 g (15%)

15 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.806-1.953 (2H, m), 2.705 (4H, t, 7.6 Hz), 3.876 (4H, s), 4.817 (2H, s), 7.112-7.319 (8H, m), 7.673-7.755 (2H, m), 7.794-7.873 (2H, m).

Reference Example 8

Synthesis of N-[4-[4-(2-chlorobenzylidene)piperidino]-butyl]phthalimide

20 1) Synthesis of 1-(tert-butoxycarbonyl)-4-(2-chlorobenzylidene)piperidine

To a solution of 9.199 g (46.168 mM) of 1-(tert-butoxycarbonyl)-4-piperidone and 19.5 g (46.2 mM) of 25 2-chlorobenzyltriphenylphosphonium chloride in 50 ml of methanol was added 8.91 g (46.2 mM) of 28% sodium methoxide-methanol at room temperature and the mixture was refluxed for 36 hours. This reaction mixture was poured in water and extracted with 2 portions of ethyl acetate. The pooled organic layer was dried over 30 Na₂SO₄ and the solvent was distilled off under reduced pressure. To the residue was added diethyl ether and the resulting precipitate (triphenylphosphine oxide) was filtered off and washed with diethyl ether. The 35 filtrate and washes were combined and the solvent was distilled off under reduced pressure. The residue was

purified by silica gel column chromatography (hexane/ethyl acetate = 9/1 to 6/1) and crystallized from cold hexane to provide the title compound.

White solid. Yield 1.473 g (10%)

5 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.474 (9H, s), 2.277-2.396 (4H, m), 3.405 (2H, t, 5.8 Hz), 3.531 (2H, t, 5.7 Hz), 6.356 (1H, s), 7.193 (3H, s), 7.354-7.402 (1H, m).

10 2) Synthesis of N-[4-[4-(2-chlorobenzylidene)piperidino]butyl]phthalimide

To a solution of 1.428 g (4.639 mM) of 1-(tert-butoxycarbonyl)-4-(2-chlorobenzylidene)piperidine in 20 ml of methanol was added 3 ml of concentrated hydrochloric acid at room temperature and the mixture 15 was stirred at 50°C for 2 hours. The solvent was then distilled off under reduced pressure to recover crude 4-(2-chlorobenzylidene)piperidine hydrochloride. This crude product was not purified but used as it was in the next reaction.

20 The above crude 4-(2-chlorobenzylidene)piperidine hydrochloride, 1.31 g (4.64 mM) of 4-bromobutylphthalimide, and 1.28 g (9.28 mM) of potassium carbonate were stirred together in 20 ml of N,N-dimethylformamide at 100°C overnight. This reaction mixture was poured in 25 water and extracted with 2 portions of ethyl acetate. The organic layers were combined and dried over MgSO₄, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1 to 30 1/1) to provide the title compound.

Yellow liquid. Yield 1.560 g (82%)

35 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.477-1.799 (4H, m), 2.341-2.438 (8H, m), 2.537 (2H, t, 5.5 Hz), 3.715 (2H, t, 6.8 Hz), 6.265 (1H, s), 7.098-7.197 (3H, m), 7.345-7.378 (1H, m), 7.682-7.748 (2H, m), 7.796-7.862 (2H, m).

Reference Example 9**Synthesis of N-[4-(4-hydroxy-4-phenylpiperidino)butyl]-phthalimide**

A mixture of 2.501 g (14.110 mM) of 4-hydroxy-4-phenylpiperidine, 3.98 g (14.1 mM) of 4-bromobutylphthalimide, and 3.90 g (28.2 mM) of potassium carbonate was stirred in 30 ml of N,N-dimethylformamide at 100°C for one day. To this reaction mixture was added water, followed by stirring, and the resulting precipitate was collected, rinsed with water, and dried to provide the title compound.

Light-yellow solid. Yield 3.835 g (72%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.507-1.768 (7H, m), 2.137 (2H, dt, 4.3 Hz, 13.0 Hz), 2.361-2.476 (4H, m), 2.773-2.830 (2H, m), 3.727 (2H, t, 6.9 Hz), 7.209-7.389 (3H, m), 7.488-7.532 (2H, m), 7.686-7.748 (2H, m), 7.801-7.863 (2H, m).

Reference Example 10**Synthesis of N-[2-hydroxy-3-(4-phenylpiperidino)propan-1-yl]phthalimide**

A solution of 1.980 g (9.744 mM) of N-(2,3-epoxypropan-1-yl)phthalimide and 1.73 g (10.7 mM) of 4-phenylpiperidine in 50 ml of ethanol was refluxed for one hour, at the end of which time the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1 to 1/1) and crystallized from diethyl ether-hexane to provide the title compound.

White solid. Yield 2.113 g (60%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.560-1.835 (4H, m), 2.083 (1H, dt, 2.8 Hz, 11.6 Hz), 2.335-2.579 (4H, m), 2.910-3.088 (2H, m), 3.730 (1H, dd, 5.0 Hz, 13.8 Hz), 3.841 (1H, dd, 6.7 Hz, 13.7 Hz), 4.004-4.130 (1H, m), 7.149-7.332 (5H, m), 7.700-7.763 (2H, m), 7.830-7.911 (2H, m).

Reference Example 11

Synthesis of N-[2-[(4-phenylpiperidino)methyl]benzyl]-phthalimide

1) Synthesis of 2-(tert-butyldimethylsilyloxyethyl)-
5 benzyl alcohol

To a solution of 14.074 g (101.86 mM) of 1,2-benzenedimethanol in 100 ml of 1,2-dimethoxyethane was added 4.07 g (102 mM) of a liquid paraffin suspension of 60% sodium hydride at room temperature and the
10 mixture was stirred at the prevailing temperature for one hour. To this reaction mixture was added a solution of 15.4 g (102 mM) of tert-butylchlorodimethylsilane in 50 ml of 1,2-dimethoxyethane dropwise, and the mixture was stirred
15 at room temperature overnight. This reaction mixture was poured in water and extracted with 3 portions of ethyl acetate. The organic layers were combined and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by
20 silica gel column chromatography (hexane/ethyl acetate = 9/1 to 3/1) to provide the title compound.

Colorless liquid. Yield 22.792 g (89%)

¹H-NMR (CDCl₃, 200 MHz) δ: 0.127 (6H, s), 0.921 (9H, s), 3.219 (1H, br t, 5.9 Hz), 4.681 (2H, d, 5.2
25 Hz), 4.807 (2H, s), 7.258-7.405 (4H, m).

2) Synthesis of N-[2-(tert-butyldimethylsilyloxyethyl)benzyl]phthalimide

To a solution of 1.413 g (45.213 mM) of 2-(tert-butyldimethylsilyloxyethyl)benzyl alcohol and 7.56 ml (54.3 mM) of triethylamine in 150 ml of diethyl ether was added 5.70 g (49.7 mM) of methanesulfonyl chloride dropwise with ice-cooling and the mixture was stirred at 0°C for 0.5 hour. This reaction mixture was poured in water and extracted with 2 portions of ethyl acetate. The organic layers were combined and dried over MgSO₄ and the solvent was distilled off under

reduced pressure. The residue was dissolved in 150 ml of N,N-dimethylformamide, followed by addition of 9.21 g (49.7 mM) of potassium phthalimide, and the mixture was stirred at 100°C for 3 hours. This reaction
5 mixture was poured in water and extracted with 3 portions of ethyl acetate. The organic layers were combined and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography
10 (hexane/ethyl acetate = 9/1) to provide the title compound.

Colorless liquid. Yield 15.021 g (87%)

¹H-NMR (CDCl₃, 200 MHz) δ: 0.112 (6H, s), 0.938 (9H,
15 s), 4.929 (2H, s), 4.971 (2H, s), 7.189-7.426 (4H,
m), 7.693-7.755 (2H, m), 7.818-7.880 (2H, m).

3) Synthesis of N-[2-(hydroxymethyl)benzyl]phthalimide
To a solution of 15.021 g (39.368 mM) of N-[2-(tert-butyldimethylsilyloxy)methyl]benzyl]phthalimide in
20 50 ml of methanol was added 5 ml of concentrated hydrochloric acid at room temperature and the mixture was stirred at the prevailing temperature for 10 minutes. This reaction mixture was poured in water-diethyl ether and the resulting precipitate was recovered, rinsed serially with water and diethyl ether, and dried to provide the title compound.
25 White solid. Yield 8.743 g (83%)

¹H-NMR (CDCl₃, 200 MHz) δ: 3.033 (1H, br s), 4.891 (2H,
30 s), 5.004 (2H, s), 7.219-7.310 (2H, m), 7.362-
7.418 (2H, m), 7.699-7.761 (2H, m), 7.809-7.871 (2H, m).

4) Synthesis of N-[2-[(4-phenylpiperidino)methyl]benzyl]phthalimide
To a solution of 2.704 g (10.117 mM) of N-[2-(hydroxymethyl)benzyl]phthalimide and 1.69 ml (12.1 mM)
35 of triethylamine in 50 ml of tetrahydrofuran was added 0.86 ml (11.1 mM) of methanesulfonyl chloride dropwise

with ice-cooling and the mixture was stirred at 0°C for 0.5 hour. This reaction mixture was poured in aqueous solution of sodium hydrogen carbonate and extracted with 3 portions of ethyl acetate. The organic layers 5 were combined and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was dissolved in 50 ml of N,N-dimethylformamide, followed by addition of 1.79 g (11.1 mM) of 4-phenylpiperidine and 2.80 g (20.2 mM) of potassium carbonate, and the 10 mixture was stirred at 100°C overnight. This reaction mixture was poured in water and extracted with 2 portions of ethyl acetate. The organic layers were combined and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was 15 purified by silica gel column chromatography (hexane/ethyl acetate = 6/1 to 3/1) to provide the title compound.

White solid. Yield 2.722 g (66%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.506-1.791 (4H, m), 2.080

20 (2H, dt, 2.3 Hz, 11.5 Hz), 2.482 (1H, tt, 3.9 Hz, 11.9 Hz), 2.989 (2H, br d, 11.4 Hz), 3.716 (2H, s), 5.123 (2H, s), 7.134-7.376 (9H, m), 7.671-7.759 (2H, m), 7.819-7.882 (2H, m).

Reference Example 12

25 Synthesis of 4-(4-phenylpiperidinomethyl)piperidine dihydrochloride

1) Synthesis of tert-butyl 4-(bromomethyl)piperidine-1-carboxylate

To a solution of 5.792 g (50.287 mM) of 4-piperidylmethanol in 150 ml of dichloromethane was 30 added 12.1 g (55.3 mM) of di-tert-butyl dicarbonate dropwise at room temperature and the mixture was stirred at the prevailing temperature overnight. The solvent was then distilled off under reduced pressure 35 to recover crude tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate. This crude

product was not purified but used as it was in the next reaction. To a solution of the above crude tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate and 18.3 g (55.3 mM) of carbon tetrabromide in 100 ml of acetonitrile was added 14.5 g (55.3 mM) of triphenylphosphine at room temperature and the mixture was stirred at the prevailing temperature for 3 hours. The solvent was then distilled off under reduced pressure. To the residue was added diethyl ether, and after stirring, the resulting precipitate (triphenylphosphine oxide) was filtered off and washed with diethyl ether. The filtrate and washes were combined and concentrated and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 30/1 to 15/1 to 9/1) to provide the title compound.

Colorless liquid. Yield 12.126 g (82%)
¹H-NMR (CDCl₃, 200 MHz) δ: 1.075-1.284 (2H, m), 1.454 (9H, s), 1.702-1.854 (3H, m), 2.693 (2H, br t, 12.5 Hz), 3.294 (2H, d, 5.8 Hz), 4.135 (2H, br d, 12.8 Hz).

2) Synthesis of tert-butyl 4-(4-phenylpiperidinomethyl)piperidine-1-carboxylate

A mixture of 3.081 g (11.075 mM) of tert-butyl 4-(bromomethyl)piperidine-1-carboxylate, 1.96 g (12.2 mM) of 4-phenylpiperidine, and 3.06 g (22.2 mM) of potassium carbonate was stirred in 20 ml of N,N-dimethylformamide at 110°C for 4 hours. This reaction mixture was poured in water and extracted with 2 portions of diethyl ether. The organic layers were combined and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1) to provide the title compound.

Yellow liquid. Yield 3.550 g (89%)

¹H-NMR (CDCl₃, 200 MHz) δ: 0.989-1.189 (2H, m), 1.460 (9H, s), 1.557-1.830 (7H, m), 1.949-2.077 (2H, m), 2.193 (2H, d, 6.6 Hz), 2.403-2.559 (1H, m), 2.696 (2H, br t, 11.9 Hz), 2.970 (2H, br d, 11.2 Hz), 4.068-4.174 (2H, m), 7.153-7.339 (5H, m).

5 3) Synthesis of 4-(4-phenylpiperidinomethyl)piperidine dihydrochloride

To a solution of 3.550 g (9.902 mM) of tert-butyl 4-(4-phenylpiperidinomethyl)piperidine-1-carboxylate in 10 30 ml of methanol was added 5 ml of concentrated hydrochloric acid and the mixture was stirred at room temperature for 3 hours. The solvent was then distilled off and the residue was crystallized from ethanol-diethyl ether to provide the title compound.

15 Light-yellow solid. Yield 2.972 g (91%)

¹H-NMR (CD₃OD, 200 MHz) δ: 1.478-1.692 (2H, m), 2.051-2.390 (7H, m), 2.835-3.233 (7H, m), 3.455 (2H, br d, 12.8 Hz), 3.752 (2H, br d, 12.8 Hz), 7.180-7.369 (5H, m).

20 Reference Example 13

Synthesis of N-[[4-(4-phenylpiperidino)cyclohexyl]methyl]phthalimide

1) Synthesis of 1,5-dibromo-3-phenylpentane

To a suspension of 9.10 g (240 mM) of lithium 25 aluminum hydride in tetrahydrofuran (500 ml)-diethyl ether (200 ml) was added a solution of 24.960 g (119.9 mM) of 3-phenylglutaric acid in 100 ml of tetrahydrofuran dropwise with ice-cooling and the mixture was stirred at room temperature overnight. To 30 this reaction mixture was added water gradually dropwise under ice-cooling until a precipitate had formed. The precipitate was filtered off with the aid of celite and washed with ethyl acetate. The filtrate and washes were pooled and the solvent was distilled 35 off under reduced pressure to provide crude 3-phenylpentane-1,5-diol. This crude product was not

purified but used as it was in the next reaction.

(Brown liquid, yield 19.19 g).

- To a solution of the crude 3-phenylpentane-1,5-diol and 74.2 g (224 mM) of carbon tetrabromide in 300 ml of acetonitrile was added 58.7 g (224 mM) of triphenylphosphine with ice-cooling and the mixture was stirred at room temperature for one hour. The solvent was then distilled off under reduced pressure and the residue was diluted with diethyl ether and stirred.
- 10 The resulting precipitate was filtered off and washed with diethyl ether. The filtrate and washes were pooled and the solvent was distilled off under reduced pressure. To the residue was added hexane, followed by stirring, and the precipitate was filtered off and washed with hexane. The filtrate and washes were combined and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 20/1) to provide the title compound.
- 15 20 Colorless liquid. Yield 25.963 g (71%)
¹H-NMR (CDCl₃, 200 MHz) δ: 2.119-2.223 (4H, m), 2.983-3.337 (5H, m), 7.176-7.386 (5H, m).
- 2) Synthesis of methyl 4-aminocyclohexanecarboxylate hydrochloride
- 25 To 5.109 g (35.680 mM) of 4-aminocyclohexane-carboxylic acid was added 50 ml of 10% HCl/methanol and the mixture was refluxed overnight. The solvent was then distilled off under reduced pressure and the residue was crystallized from methanol-diethyl ether to provide the title compound.
- 30 White solid. Yield 6.624 g (96%)
¹H-NMR (CD₃OD, 200 MHz) δ: 1.460-1.936 (6H, m), 2.073-2.187 (3H, m), 2.639-2.702 (1H, m), 3.187 (1H, br s), 3.696 (3H, s).
- 35 3) Synthesis of methyl 4-(4-phenylpiperidino)cyclohexanecarboxylate

A solution of 3.896 g (20.117 mM) of methyl 4-aminocyclohexanecarboxylate hydrochloride, 6.77 g (22.1 mM) of 1,5-dibromo-3-phenylpentane, and 14.0 ml (80.5 mM) of N,N-diisopropylethylamine in 100 ml of acetonitrile was refluxed for one day. This reaction mixture was poured in aqueous solution of sodium hydrogen carbonate and extracted with 3 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1 to 1/1) to provide the title compound. Yellow liquid. Yield 2.825 g (47%).
¹H-NMR (CDCl₃, 200 MHz) δ: 1.294-1.811 (10H, m), 2.046-2.609 (7H, m), 3.034 (2H, d, 11.4 Hz), 3.668 (0.6H, s), 3.691 (2.4H, s), 7.150-7.336 (5H, m).

4) Synthesis of 4-(4-phenylpiperidino)cyclohexylmethanol

To a suspension of 0.36 g (9.37 mM) of lithium aluminum hydride in 50 ml of tetrahydrofuran was added a solution of 2.825 g (9.372 mM) of methyl 4-(4-phenylpiperidino)cyclohexanecarboxylate in 50 ml of tetrahydrofuran dropwise with ice-cooling and the mixture was stirred at room temperature for one hour. To this reaction mixture was added ethyl acetate with ice-cooling to decompose the excess lithium aluminum hydride. Then, water was added until a white precipitate had formed. The precipitate was filtered off with the aid of celite and washed with ethyl acetate. The filtrate and washes were pooled and the solvent was distilled off under reduced pressure. The solid residue was rinsed with diethyl ether-hexane to provide the title compound.

White solid. Yield 2.160 g (84%).
¹H-NMR (CDCl₃, 200 MHz) δ: 0.885-2.007 (15H, m), 2.108-2.553 (4H, m), 3.013-3.123 (2H, m), 3.460 (0.4H,

d, 6.2 Hz), 3.611 (1.6H, d, 6.6 Hz), 7.140-7.341 (5H, m).

5) Synthesis of N-[(4-(4-phenylpiperidino)cyclohexyl)-methyl]phthalimide

5 To a solution of 1.986 g (7.264 mM) of 4-(4-phenylpiperidino)cyclohexylmethanol and 1.21 ml (8.72 mM) of triethylamine in 50 ml of tetrahydrofuran was added 0.62 ml (7.99 mM) of methanesulfonyl chloride dropwise with ice-cooling and the mixture was stirred
10 at 0°C for 5 hours. This reaction mixture was poured in water and extracted with 2 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was dissolved in 50 ml of N,N-dimethylformamide, followed by addition of 1.48 g (7.99 mM) of potassium phthalimide, and the mixture was stirred at 100°C overnight. After cooling to room temperature, this reaction mixture was poured in water and stirred and the resulting precipitate was collected
15 by filtration, rinsed with water, and dried to provide the title compound.

20 Light-brown solid. Yield 0.567 g (19%)

25 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.000-1.368 (2H, m), 1.669-1.958 (12H, m), 2.238-2.517 (3H, m), 2.885-3.150 (2H, m), 3.545 (1.6H, d, 6.6 Hz), 3.699 (0.4H, d, 7.6 Hz), 7.140-7.325 (5H, m), 7.695-7.757 (2H, m), 7.808-7.873 (2H, m).

Reference Example 14

30 Synthesis of N-(1-benzhydrylpiperidin-4-ylmethyl)phthalimide

1) Synthesis of 1-benzhydrylpiperidin-4-ylmethanol

In 20 ml of N,N-dimethylformamide, 2.291 g (15.108 mM) of 4-piperidylmethanol hydrochloride, 4.48 g (18.1 mM) of bromodiphenylmethane, and 6.26 g (45.3 mM) of potassium carbonate were stirred together at 100°C for 3.5 days and, then, at 150°C for 2 hours. After

cooling to room temperature, this reaction mixture was poured in water and extracted with 2 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1 to 2/1 to 1/1) to provide the title compound.

5 White solid. Yield 0.347 g (8.2%)

10 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.209-1.696 (6H, m), 1.841
(2H, t, 11.7 Hz), 2.910 (2H, d, 12.2 Hz), 3.500
(2H, br s), 4.235 (1H, s), 7.127-7.305 (6H, m),
7.385-7.426 (4H, m).

15 2) Synthesis of N-(1-benzhydrylpiperidin-4-ylmethyl)-phthalimide

20 To a solution of 0.450 g (1.599 mM) of 1-benzhydrylpiperidin-4-ylmethanol and 0.33 ml (2.40 mM) of triethylamine in 30 ml of tetrahydrofuran was added 0.15 ml (1.92 mM) of methanesulfonyl chloride dropwise with ice-cooling and the mixture was stirred at 0°C for 0.5 hour. This reaction mixture was poured in water and extracted with 2 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was dissolved in 25 ml of N,N-dimethylformamide, followed by addition of 0.36 g (1.92 mM) of potassium phthalimide, and the mixture was stirred at 100°C overnight. After cooling to room temperature, this reaction mixture was poured in water and extracted with 2 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 6/1 to 3/1) and crystallized from diethyl ether-hexane to provide the title compound.

30 35 White solid. Yield 0.178 g (27%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.291-1.496 (2H, m), 1.596
(2H, br d, 13.0 Hz), 1.683-1.846 (3H, m), 2.868
(2H, d, 11.8 Hz), 3.595 (2H, d, 7.0 Hz), 4.222
(1H, s), 7.101-7.286 (6H, m), 7.345-7.456 (4H, m),
5 7.643-7.735 (2H, m), 7.782-7.867 (2H, m).

Reference Example 15

Synthesis of 1-(4-aminobutan-1-yl)-4-phenylpiperidine

1) Synthesis of 4-(4-phenylpiperidin-1-yl)butan-1-ylphthalimide

10 A solution of 5.00 g (31 mM) of 4-phenylpiperidine, 8.75 g (31 mM) of N-(4-bromobutyl)phthalimide, and 6.5 ml (46.6 mM) of triethylamine in acetonitrile (30 ml) was refluxed under nitrogen for 62 hours. The solvent was then
15 distilled off under reduced pressure and the residue was diluted with water and extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The resulting crude product was purified by column chromatography (methanol-ethyl acetate 5-10%) to provide the title compound.

White solid. Yield 10.38 g (92%)

1¹H-NMR (200 MHz, CDCl₃) δ: 1.49-1.88 (m, 8H), 1.95-2.14
(m, 2H), 2.32-2.57 (m, 3H), 3.04 (br d, J=11.4 Hz,
25 2H), 3.73 (d, J=6.8 Hz, 2H), 7.11-7.35 (m, 5H),
7.65-7.76 (m, 2H), 7.78-7.90 (m, 2H).

2) Synthesis of 1-(4-aminobutan-1-yl)-4-phenylpiperidine

30 To a solution of 10.38 g (28.64 mM) of 4-(4-phenylpiperidin-1-yl)butan-1-ylphthalimide in ethanol (160 ml) was added 4.2 ml (86.58 mM) of hydrazine monohydrate at room temperature and the mixture was refluxed for 1.5 hours. The white solid that formed was filtered off and the solvent was distilled off
35 under reduced pressure. The residue was diluted with aqueous solution of sodium hydroxide and extracted with

chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The solvent was then distilled off under reduced pressure to provide the title compound.

5 Light-yellow solid. Yield 6.49 g (98%)

¹H-NMR (200 MHz, CDCl₃) δ: 1.39-1.63 (m, 4H), 1.72-1.90 (m, 6H), 2.35-2.58 (m, 3H), 2.73 (t, J=6.6 Hz, 2H), 3.07 (br d, J=11.6 Hz, 2H), 7.15-7.35 (m, 5H).

10 Reference Example 16

Synthesis of 1-(3-aminopropan-1-yl)-4-phenylpiperidine

1) The procedure of Reference Example 15-1) was generally followed to provide 3-(4-phenylpiperidin-1-yl)propan-1-ylphthalimide as white solid.

15 ¹H-NMR (200 MHz, CDCl₃) δ: 1.40-1.79 (m, 4H), 1.83-2.04 (m, 4H), 2.30-2.51 (m, 1H), 2.45 (t, J=6.9 Hz, 2H), 2.90-3.05 (m, 2H), 3.79 (t, J=7.0 Hz, 2H), 7.03-7.32 (m, 5H), 7.66-7.76 (m, 2H), 7.80-7.90 (m, 2H).

20 2) The procedure of Reference Example 15-2) was generally followed to provide 1-(3-aminopropan-1-yl)-4-phenylpiperidine as white solid.

25 ¹H-NMR (200 MHz, CDCl₃) δ: 1.61-1.90 (m, 6H), 1.94-2.12 (m, 2H), 2.29-2.59 (m, 5H), 2.81 (t, J=6.8 Hz, 2H), 3.00-3.15 (m, 2H), 7.07-7.38 (m, 5H).

Reference Example 17

Synthesis of 1-(4-aminobutan-1-yl)-4-benzylpiperidine dihydrochloride

1) The procedure of Reference Example 15-1) was generally followed to provide 4-(4-benzylpiperidin-1-yl)butan-1-ylphthalimide as yellow oil.

30 ¹H-NMR (200 MHz, CDCl₃) δ: 1.17-1.96 (m, 11H), 2.26-2.38 (m, 2H), 2.51 (d, J=6.6 Hz, 2H), 2.83-2.96 (m, 2H), 3.70 (t, J=6.8 Hz, 2H), 7.10-7.31 (m, 5H), 7.67-7.73 (m, 2H), 7.78-7.86 (m, 2H).

35 2) Synthesis of 1-(4-aminobutan-1-yl)-4-

benzylpiperidine dihydrochloride

To a solution of 9.66 g (25.7 mM) of 4-(4-benzyl-piperidine-1-yl)butan-1-ylphthalimide in ethanol (30 ml) was added 1.9 ml (39.2 mM) of hydrazine monohydrate at room temperature and the mixture was refluxed for 2 hours. The white solid that formed was filtered off and the solvent was distilled off under reduced pressure. The residue was diluted with aqueous solution of sodium hydroxide and extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The solvent was then distilled off under reduced pressure to provide a crude product (free compound). To a solution of this free compound (6.39 g) in ethanol (30 ml) was added 12N-hydrochloric acid (10 ml) at room temperature, followed by a few minutes' stirring. The solvent was then distilled off under reduced pressure and diethyl ether was added. The crystals that formed were collected by filtration and rinsed with ethanol and diethyl ether to provide the title compound.

White crystals. Yield 5.84 g (71%)

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.50-1.88 (m, 9H), 2.68-3.50 (m, 10H), 7.14-7.36 (m, 5H), 7.92-8.24 (m, 2H).

Reference Example 18**Synthesis of 1-(3-aminopropan-1-yl)-4-benzylpiperidine dihydrochloride**

1) The procedure of Reference Example 15-1) was generally followed to provide 3-(4-benzylpiperidin-1-yl)propan-1-ylphthalimide as white solid.

¹H-NMR (200 MHz, CDCl₃) δ: 0.94-1.19 (m, 2H), 1.29-1.95 (m, 7H), 2.30-2.47 (m, 4H), 2.76-2.89 (m, 2H), 3.74 (t, J=6.8 Hz, 2H), 7.04-7.32 (m, 5H), 7.65-7.77 (m, 2H), 7.80-7.90 (m, 2H).

2) Synthesis of 1-(3-aminopropan-1-yl)-4-

benzylpiperidine dihydrochloride

To a solution of 9.22 g (25.4 mM) of 3-(4-benzyl-piperidin-1-yl)propan-1-ylphthalimide in ethanol (50 ml) was added 1.8 ml (37.1 mM) of hydrazine monohydrate at room temperature for 3 hours. After the white solid that formed was filtered off, 12.0 ml (52.2 mM) of di-tert-butyl dicarbonate was added and the mixture was stirred at room temperature for 14 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The solvent was then distilled off under reduced pressure and the crude product was purified by column chromatography (methanol-ethyl acetate 10-20%). To this free compound was added 12N-hydrochloric acid (8 ml) at room temperature, followed by a few minutes' stirring. To this reaction mixture was added ethanol and the solvent was then distilled off under reduced pressure. The residue was treated with diethyl ether and the resulting crystals were collected by filtration and rinsed with ethanol and diethyl ether to provide the title compound.

White crystals. Yield 3.11 g (40%)

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.44-1.85 (m, 4H), 1.93-2.11 (m, 2H), 2.70-2.96 (m, 4H), 3.01-3.47 (m, 6H), 7.13-7.37 (m, 5H), 8.02-8.36 (m, 2H).

Reference Example 19

Synthesis of 1-(4-aminobutan-1-yl)-4-phenylpiperazine trihydrochloride

1) The procedure of Reference Example 15-1) was generally followed to provide 4-(4-phenylpiperazin-1-yl)butan-1-ylphthalimide as yellow-green crystals.

¹H-NMR (200 MHz, CDCl₃) δ: 1.49-1.83 (m, 4H), 2.44 (t, J=7.3 Hz, 2H), 2.57 (m, 4H), 3.13-3.25 (m, 4H), 3.73 (t, J=6.9 Hz, 2H), 6.81-6.97 (m, 3H), 7.18-

7.32 (m, 2H), 7.66-7.78 (m, 2H), 7.78-7.90 (m, 2H).

2) The procedure of Reference Example 17-2) was generally followed to provide 1-(4-aminobutan-1-yl)-4-phenylpiperazine trihydrochloride as white crystals.

5 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.54-1.95 (m, 4H), 2.70-2.91 (m, 2H), 2.98-3.31 (m, 6H), 3.45-3.60 (m, 2H), 3.69-3.1 (m, 2H), 5.65-6.03 (m, 3H), 6.84-6.91 (m, 1H), 7.00-7.04 (m, 2H), 7.24-7.32 (m, 2H).

10

Reference Example 20

Synthesis of 1-(3-aminopropan-1-yl)-4-phenylpiperazine trihydrochloride

1) The procedure of Reference Example 15-1) was generally followed to provide 3-(4-phenylpiperazin-1-yl)-propan-1-ylphthalimide as white crystals.

15 ¹H-NMR (200 MHz, CDCl₃) δ: 1.82-1.98 (m, 2H), 2.43-2.59 (m, 6H), 2.99-3.10 (m, 4H), 3.80 (t, J=7.0 Hz, 2H), 6.78-6.91 (m, 3H), 7.17-7.30 (m, 2H), 7.64-7.75 (m, 2H), 7.79-7.90 (m, 2H).

20 2) The procedure of Reference Example 17-2) was generally followed to provide 1-(3-aminopropan-1-yl)-4-phenylpiperazine trihydrochloride as white crystals.

25 ¹H-NMR (200 MHz, DMSO-d₆) δ: 2.00-2.21 (m, 2H), 2.82-3.02 (m, 2H), 3.02-3.35 (m, 6H), 3.44-3.61 (m, 2H), 3.72-3.90 (m, 2H), 5.86-6.25 (m, 3H), 6.81-6.93 (m, 1H), 6.95-7.06 (m, 2H), 7.20-7.32 (m, 2H), 8.12-8.38 (m, 2H).

Reference Example 21

30 Synthesis of 1-(4-aminobutan-1-yl)-4-benzylpiperazine trihydrochloride

1) The procedure of Reference Example 15-1) was generally followed to provide 4-(4-benzylpiperazin-1-yl)-butan-1-ylphthalimide as tan-colored oil.

35 ¹H-NMR (200 MHz, CDCl₃) δ: 1.45-1.79 (m, 4H), 2.31-2.57 (m, 10H), 3.49 (s, 2H), 3.70 (t, J=6.9 Hz, 2H),

7.22-7.35 (m, 5H), 7.68-7.76 (m, 2H), 7.80-7.87 (m, 2H).

2) The procedure of Reference Example 17-2) was generally followed to provide 1-(4-aminobutan-1-yl)-4-
5 benzylpiperazine trihydrochloride as white crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.50-1.88 (m, 4H), 2.66-
2.87 (m, 2H), 2.95-3.77 (m, 10H), 4.17-4.52 (m,
2H), 7.35-7.51 (m, 3H), 7.55-7.72 (m, 2H), 7.92-
8.25 (m, 2H).

10 Reference Example 22

Synthesis of 1-(3-aminopropan-1-yl)-4-benzylpiperazine trihydrochloride

1) The procedure of Reference Example 15-1) was generally followed to provide 3-(4-benzylpiperazin-1-
15 yl)-propan-1-ylphthalimide as tan-colored oil.

¹H-NMR (200 MHz, CDCl₃) δ: 1.78-1.93 (m, 2H), 2.23-2.53
(m, 10H), 3.40 (s, 2H), 3.75 (t, J=6.8 Hz, 2H),
7.19-7.31 (m, 5H), 7.65-7.76 (m, 2H), 7.78-7.88
(m, 2H).

20 2) The procedure of Reference Example 17-2) was generally followed to provide 1-(3-aminopropan-1-yl)-4-
benzylpiperazine trihydrochloride as white crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.93-2.13 (m, 2H), 2.80-
3.01 (m, 2H), 3.11-3.93 (m, 10H), 4.29-4.52 (m,
2H), 7.41-7.52 (m, 3H), 7.59-7.73 (m, 2H), 8.00-
8.28 (m, 2H).

Reference Example 23

Synthesis of 2-(4-aminobutan-1-yl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride

30 1) The procedure of Reference Example 15-1) was generally followed to provide 4-(1,2,3,4-tetrahydroisoquinolin-2-yl)-butan-1-ylphthalimide as yellow solid.

¹H-NMR (200 MHz, CDCl₃) δ: 1.54-1.93 (m, 4H), 2.54 (t,
35 J=7.4 Hz, 2H), 2.69-2.74 (m, 2H), 2.86-2.92 (m,
2H), 3.61 (s, 2H), 3.70 (t, J=7.0 Hz, 2H), 6.94-

7.14 (m, 4H), 7.64-7.75 (m, 2H), 7.78-7.89 (m, 2H).

2) The procedure of Reference Example 17-2) was generally followed to provide 2-(4-aminobutan-1-yl)-
5 1,2,3,4-tetrahydroisoquinoline dihydrochloride as white crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.52-1.75 (m, 2H), 1.79-
2.01 (m, 2H), 2.71-3.75 (m, 8H), 4.17-4.35 (m, 1H), 4.40-4.58 (m, 1H), 7.13-7.32 (m, 4H), 7.98-
10 8.29 (m, 3H), 11.10-11.32 (m, 1H).

Reference Example 24

Synthesis of 2-(3-aminopropan-1-yl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride

1) The procedure of Reference Example 15-1) was generally followed to provide 3-(1,2,3,4-tetrahydroisoquinolin-2-yl)-propan-1-ylphthalimide as white crystals.

¹H-NMR (200 MHz, CDCl₃) δ: 1.88-2.05 (m, 2H), 2.60 (t, J=7.0 Hz, 2H), 2.64-2.72 (m, 2H), 2.73-2.83 (m, 2H), 3.57 (s, 2H), 3.82 (t, J=7.0 Hz, 2H), 6.92-7.12 (m, 4H), 7.58-7.67 (m, 2H), 7.72-7.81 (m, 2H).

2) The procedure of Reference Example 17-2) was generally followed to provide 2-(3-aminopropan-1-yl)-
25 1,2,3,4-tetrahydroisoquinoline dihydrochloride as white crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 2.03-2.26 (m, 2H), 2.82-3.13 (m, 2H), 3.17-3.75 (m, 6H), 4.18-4.36 (m, 1H), 4.44-4.61 (m, 1H), 7.12-7.38 (m, 4H), 8.02-8.45 (m, 3H).

Reference Example 25

Synthesis of 3-(1-tert-butoxycarbonyl-4-piperidyl)-1-propylamine

1) Synthesis of 3-(1-tert-butoxycarbonyl-4-piperidyl)-
35 1-propanol

To a solution of 35.8 g (250 mM) of 3-(4-

5 piperidyl)-1-propanol in 500 ml of ethanol was added 54.6 g (250 mM) of di-tert-butyl dicarbonate dropwise and the mixture was stirred at room temperature for one hour. The solvent was then distilled off under reduced pressure and the residue was purified by column chromatography (ethyl acetate-hexane = 1/1 ethyl acetate) to provide the title compound as light-yellow oil (50.2 g, 82%).

10 $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 0.96-1.41 (m, 5H), 1.45 (s, 9H), 1.49-1.78 (m, 4H), 2.61-2.74 (m, 2H), 3.62 (t, $J=6.4$ Hz, 2H), 4.04-4.10 (m, 2H).

2) Synthesis of 3-(1-tert-butoxycarbonyl-4-piperidyl)-1-propylphthalimide

15 To a solution of 4.87 g (20.0 mM) of 3-(1-tert-butoxycarbonyl-4-piperidyl)-1-propanol and 5.6 ml (40.0 mM) of triethylamine in 50 ml of diethyl ether was added 1.86 ml (24.0 mM) of methanesulfonyl chloride at 0°C and the mixture was stirred at 0°C for 30 minutes. This reaction mixture was then poured in iced water and extracted with ether. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO_4 , and the solvent was distilled off under reduced pressure to provide 3-(1-tert-butoxycarbonyl-4-piperidyl)-1-propyl mesylate. To a 20 solution of the above mesylate in 100 ml of N,N-dimethylformamide was added 3.70 g (20.0 mM) of potassium phthalimide and the mixture was heated at 100°C for 90 minutes. After cooling to room temperature, this reaction mixture was poured in iced water and the resulting precipitate was collected by filtration, rinsed with water, and dried in vacuo to provide the title compound as white solid (20.24 g, 90%).

25 $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 0.94-1.37 (m, 5H), 1.45 (s, 9H), 1.57-1.80 (m, 4H), 2.61-2.73 (m, 2H), 3.68 (t, $J=7.2$ Hz, 2H), 4.04-4.10 (m, 2H), 7.70-7.87

(m, 4H).

3) Synthesis of 3-(1-tert-butoxycarbonyl-4-piperidyl)-1-propylamine

To a solution of 20.24 g (54.34 mM) of 3-(1-tert-butoxycarbonyl-4-piperidyl)-1-propylphthalimide in 350 ml of ethanol was added 7.9 ml (163 mM) of hydrazine monohydrate and the mixture was refluxed for one hour. After cooling to room temperature, the resulting precipitate (phthalide) was filtered off and washed with a small amount of ethanol. The filtrate and washes were pooled and the solvent was distilled off under reduced pressure. The residue was extracted with chloroform and the organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The solvent was then distilled off under reduced pressure to provide the title compound.

Light-yellow oil. Yield 13.08 g (99%)

¹H-NMR (200 MHz, CDCl₃) δ: 0.96-1.95 (m, 18H), 2.61-2.72 (m, 4H), 4.04-4.10 (m, 2H).

20 Reference Example 26

Synthesis of tert-butyl 4-

[(methylamino)methyl]piperidine-1-carboxylate

1) Synthesis of N-(1-tert-butoxycarbonylpiperidin-4-ylmethyl)trifluoroacetamide

25 To a solution of 5.07 g (23.7 mM) of tert-butyl 4-aminomethylpiperidine-1-carboxylate and 5.0 ml (35.9 mM) of triethylamine in acetonitrile (40 ml) was added 5.6 ml (47.1 mM) of ethyl trifluoroacetate at room temperature and the mixture was stirred at room temperature for 1.5 hours. After the solvent was distilled off under reduced pressure, the residue was diluted with ethyl acetate and washed with water and saturated aqueous solution of sodium chloride. The solvent was then distilled off under reduced pressure to provide the title compound as light-yellow solid (6.40 g, 87%).

¹H-NMR (200 MHz, CDCl₃) δ: 1.04-1.30 (m, 2H), 1.45 (s, 9H), 1.60-1.82 (m, 3H), 2.62-2.76 (m, 2H), 2.78 (t, J=6.4 Hz, 2H), 4.07-4.18 (m, 2H), 6.33-6.48 (m, 1H).

5 2) Synthesis of N-methyl-N-(1-tert-butoxycarbonyl-piperidin-4-ylmethyl)trifluoroacetamide

Under nitrogen, 0.21 g (5.25 mM) of 60% sodium hydride-liquid paraffin was added to a solution of 1.51 g (4.87 mM) of N-(1-tert-butoxycarbonylpiperidin-4-yl-

10 methyl)trifluoroacetamide in N,N-dimethylformamide (10 ml) at 0°C and the mixture was stirred at the prevailing temperature for 40 minutes. To this reaction mixture was added 0.5 ml (5.90 mM) of methyl methanesulfonate and the mixture was stirred at room

15 temperature for 112 hours. The mixture was further stirred at 100°C for 2.5 hours, at the end of which time the reaction was stopped by adding saturated aqueous solution of sodium hydrogen carbonate. The reaction mixture was then extracted with ethyl acetate.

20 The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The crude product thus obtained was purified by column chromatography (ethyl acetate-hexane 40%) to provide the title compound.

25 Colorless oil. Yield 1.32 g (84%)

¹H-NMR (200 MHz, CDCl₃) δ: 1.10-1.30 (m, 2H), 1.46 (s, 9H), 1.50-1.96 (m, 3H), 2.56-2.77 (m, 2H), 3.04 (s, 0.78 H), 3.15 (s, 2.22H), 3.26-3.40 (m, 2H), 4.04-4.25 (m, 2H).

30 3) Synthesis of tert-butyl 4-[(methylamino)methyl]-piperidine-1-carboxylate

To a solution of 1.32 g (4.07 mM) of N-methyl-N-(1-tert-butoxycarbonylpiperidin-4-

35 ylmethyl)trifluoroacetamide in ethanol was added 0.23 g (6.08 mM) of sodium borohydride at room temperature and the mixture was stirred at room temperature for 2.5

hours. To this reaction mixture was further added 0.27 g (7.1 mM) of sodium borohydride and the mixture was stirred at room temperature for 20 hours. The mixture was then stirred at 60°C for 1.5 hours. To this

5 reaction mixture was added water to stop the reaction and methylene chloride was added for extraction. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The solvent was then distilled off to provide the title
10 compound as colorless oil (1.00 g, quantitative).

¹H-NMR (200 MHz, CDCl₃) δ: 0.96-1.24 (m, 2H), 1.45 (s, 9H), 1.50-1.78 (m, 3H), 2.44 (s, 3H), 2.47 (d, J=6.2 Hz, 2H), 2.63-2.76 (m, 2H), 3.98-4.21 (m, 2H).

15 Reference Example 27

Synthesis of tert-butyl 4-[(benzylamino)methyl]piperidin-1-carboxylate

1) The procedure of Reference Example 26-2) was generally followed to provide N-benzyl-N-[1-(tert-
20 butoxycarbonyl)piperidin-4-ylmethyl]trifluoroacetamide as colorless oil.

¹H-NMR (200 MHz, CDCl₃) δ: 1.02-1.30 (m, 2H), 1.44 (s, 9H), 1.50-1.63 (m, 2H), 1.69-1.99 (m, 1H), 2.52-2.74 (m, 2H), 3.98-4.24 (m, 2H), 4.59-4.72 (m, 2H), 7.16-7.42 (m, 5H).

2) The procedure of Reference Example 26-3) was generally followed to provide tert-butyl 4-(benzylamino)methylpiperidine-1-carboxylate as colorless oil.

30 ¹H-NMR (200 MHz, CDCl₃) δ: 0.96-1.23 (m, 2H), 1.45 (s, 9H), 1.47-1.78 (m, 3H), 2.51 (d, J=6.4 Hz, 2H), 2.54-2.78 (m, 2H), 3.79 (s, 2H), 3.95-4.18 (m, 2H), 7.19-7.44 (m, 5H).

Reference Example 28

35 Synthesis of 2-[N-tert-butoxycarbonyl-N-(3-phenylpropan-1-yl)]aminoethylamine

1) Synthesis of 2-[N-tert-butoxycarbonyl-N-(3-phenylpropan-1-yl)]aminoethanol

A solution of 7.6 ml (50 mM) of 3-bromo-1-phenylpropane and 17.1 g (280 mM) of 2-aminoethanol in acetonitrile (100 ml) was refluxed for 16 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with chloroform and washed with water and saturated aqueous solution of sodium chloride. The organic layer was dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform (100 ml), followed by addition of 11.5 ml (50 mM) of di-tert-butyl dicarbonate, and the mixture was stirred at room temperature for 2 hours. The solvent was distilled off under reduced pressure and the residue was purified by column chromatography (ethyl acetate-hexane 50%) to provide the title compound.

Yield 14.07 g (quantitative)

¹H-NMR (200 MHz, CDCl₃) δ: 1.45 (s, 9H), 1.73-1.95 (m, 2H), 2.61 (t, J=7.8 Hz, 2H), 3.15-3.44 (m, 4H), 3.67-3.80 (m, 2H), 7.12-7.35 (m, 5H).

2) Synthesis of 2-[N-tert-butoxycarbonyl-N-(3-phenylpropan-1-yl)]aminoethylphthalimide

To a suspension of 14.07 g (50 mM) of 2-[N-tert-butoxycarbonyl-N-(3-phenylpropan-1-yl)]aminoethanol, 26.23 g (100 mM) of triphenylphosphine, and 14.71 g (100 mM) of phthalimide in tetrahydrofuran (100 ml) was added 15.8 ml (100 mM) of diethyl azodicarboxylate at 0°C and the mixture was stirred for 4.5 hours. The solvent was then distilled off under reduced pressure and diethyl ether was added to the residue, followed by cooling. The resulting crystals were filtered off and the solvent was distilled off under reduced pressure. The residue was purified by column chromatography (ethyl acetate-hexane 20-30%) to provide the title compound.

Yield 13.34 g (65%)

¹H-NMR (200 MHz, CDCl₃) δ: 1.24-1.30 (s, 9H), 1.74-1.95 (m, 2H), 2.59 (t, J=7.8 Hz, 2H), 3.13-3.36 (m, 2H), 3.41-3.55 (m, 2H), 3.76-3.90 (m, 2H), 7.09-7.32 (m, 5H), 7.63-7.92 (m, 4H).

5 3) Synthesis of 2-[N-tert-butoxycarbonyl-N-(3-phenylpropan-1-yl)aminoethyl]amine

To a solution of 13.34 g (32.5 mM) of 2-[N-tert-butoxycarbonyl-N-(3-phenylpropan-1-yl)]aminoethylphthalimide in ethanol (200 ml) was added 4.8 ml (99 mM) of hydrazine monohydrate at room temperature and the mixture was refluxed for 1.5 hours. After cooling to room temperature, the precipitate was filtered off and the solvent was distilled off under reduced pressure. The residue was diluted with water and extracted with chloroform and the organic layer was washed with saturated aqueous solution of sodium chloride. The solvent was then distilled off under reduced pressure to provide the title compound in crude form as light-yellow oil.

20 Yield 9.84 g (quantitative)

¹H-NMR (200 MHz, CDCl₃) δ: 1.44 (s, 9H), 1.74-1.94 (m, 2H), 2.60 (t, J=7.8 Hz, 2H), 2.81 (t, J=6.6 Hz, 2H), 3.11-3.35 (m, 4H), 7.13-7.35 (m, 5H).

25 Reference Example 29

Synthesis of 3-[N-tert-butoxycarbonyl-N-(3-phenylpropan-1-yl)]aminopropylamine

1) The procedure of Reference Example 28-1) was generally followed to provide 3-[N-tert-butoxycarbonyl-N-(3-phenylpropan-1-yl)]aminopropanol.

¹H-NMR (200 MHz, CDCl₃) δ: 1.45 (s, 9H), 1.55-1.94 (m, 4H), 2.54-2.66 (m, 2H), 3.06-3.22 (m, 2H), 3.29-3.43 (m, 2H), 3.46-3.62 (m, 2H), 7.12-7.33 (m, 5H).

35 2) The procedure of Reference Example 28-2) was generally followed to provide 3-[N-tert-butoxycarbonyl-

N-(3-phenylpropan-1-yl)aminopropylphthalimide.

¹H-NMR (200 MHz, CDCl₃) δ: 1.41 (s, 9H), 1.78-1.96 (m, 4H), 2.55-2.63 (m, 2H), 3.13-3.31 (m, 4H), 3.68 (t, J=7.4 Hz, 2H), 7.12-7.31 (m, 5H), 7.68-7.87 (m, 4H).

5 3) The procedure of Reference Example 28-3) was generally followed to provide 3-[N-tert-butoxycarbonyl-N-(3-phenylpropan-1-yl)]aminopropylamine as light-yellow oil.

10 ¹H-NMR (200 MHz, CDCl₃) δ: 1.44 (s, 9H), 1.52-1.95 (m, 4H), 2.56-2.72 (m, 4H), 3.10-3.35 (m, 4H), 7.14-7.35 (m, 5H).

Reference Example 30

Synthesis of 4-[N-tert-butoxycarbonyl-N-(3-phenylpropan-1-yl)]aminobutylamine

15 1) The procedure of Reference Example 28-1) was generally followed to provide 4-[N-tert-butoxycarbonyl-N-(3-phenylpropan-1-yl)]aminobutanol.

19 ¹H-NMR (200 MHz, CDCl₃) δ: 1.44 (s, 9H), 1.47-1.65 (m, 4H), 1.74-1.95 (m, 2H), 2.60 (t, J=7.8 Hz, 2H), 3.11-3.29 (m, 4H), 3.60-3.72 (m, 2H), 7.12-7.33 (m, 5H).

20 2) The procedure of Reference Example 28-2) was generally followed to provide 4-[N-tert-butoxycarbonyl-N-(3-phenylpropan-1-yl)]aminobutylphthalimide.

25 ¹H-NMR (200 MHz, CDCl₃) δ: 1.42 (s, 9H), 1.47-1.92 (m, 6H), 2.54-2.62 (m, 2H), 3.09-3.27 (m, 4H), 3.70 (t, J=6.8 Hz, 2H), 7.10-7.32 (m, 5H), 7.68-7.89 (m, 4H).

30 3) The procedure of Reference Example 28-3) was generally followed to provide 4-[N-tert-butoxycarbonyl-N-(3-phenylpropan-1-yl)]aminobutylamine as light-yellow oil.

35 ¹H-NMR (200 MHz, CDCl₃) δ: 1.43 (s, 9H), 1.35-1.62 (m, 4H), 1.72-1.90 (m, 2H), 2.20-2.93 (m, 4H), 3.08-3.31 (m, 4H), 7.13-7.34 (m, 5H).

Reference Example 31

Synthesis of 3-[N-methyl-N-(3-phenylpropan-1-yl)amino]-propan-1-ylamine

1) Synthesis of N-(3-phenylpropan-1-yl)trifluoroacetamide

To a solution of 9.37 g (69.3 mM) of 3-phenylpropylamine and 14 ml (100.4 mM) of triethylamine in acetonitrile (70 ml) was added 16.4 ml (122.7 mM) of ethyl trifluoroacetate at room temperature and the mixture was stirred at the prevailing temperature for 2 hours. The solvent was then distilled off and the residue was diluted with ethyl acetate and washed with water and saturated aqueous solution of sodium chloride. The organic layer was dried over MgSO_4 and the solvent was distilled off under reduced pressure to provide the title compound.

White crystals. Yield 15.95 g (quantitative)

$^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 1.86-2.04 (m, 2H), 2.69 (t, $J=7.5$ Hz, 2H), 3.39 (dd, $J=6.6$, 6.6 Hz, 2H), 6.16-6.43 (m, 1H), 7.09-7.41 (m, 5H).

2) Synthesis of N-methyl-N-(3-phenylpropan-1-yl)trifluoroacetamide

Under nitrogen, 1.5 g (37.5 mM) of a 60% suspension of sodium hydride in liquid paraffin was added to a solution of 8.0 g (34.6 mM) of N-(3-phenylpropan-1-yl)trifluoroacetamide in $\text{N,N-dimethylformamide}$ (70 ml) at 0°C and the mixture was stirred at the prevailing temperature for 40 minutes. To this reaction mixture was added 3.5 ml (41.3 mM) of methyl methanesulfonate and the mixture was stirred at room temperature for 1.5 hours. Then, water was added to the reaction system to stop the reaction and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over MgSO_4 , and purified by column chromatography (ethyl acetate-hexane

15%) to provide the title compound.

Light-yellow oil. Yield 7.48 g (88%)

¹H-NMR (200 MHz, CDCl₃) δ: 1.83-2.02 (m, 2H), 2.61-2.69
5 (m, 2H), 3.00 (s, 1.17H), 3.09 (s, 1.83H), 3.35-
3.52 (m, 2H), 7.14-7.37 (m, 5H).

3) Synthesis of 3-[N-methyl-N-(3-phenylpropan-1-yl)amino]propan-1-ylphthalimide

To a solution of 4.0 g (16.3 mM) of N-methyl-N-(3-phenylpropan-1-yl)trifluoroacetamide in ethanol (30 ml) was added 1.23 g (32.5 mM) of sodium borohydride at room temperature and the mixture was stirred at the prevailing temperature for 15 hours. This reaction mixture was diluted with water and extracted with methylene chloride. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The solvent was then distilled off under reduced pressure to provide crude (3-phenylpropan-1-yl)methylamine (2.5 g) as light-yellow oil. A solution of 2.6 g (<16.3 mM) of this (3-phenylpropan-1-yl)methylamine, 4.81 g (17.9 mM) of N-(3-bromopropyl)phthalimide, and 3.0 ml (21.5 mM) of triethylamine was refluxed for 20 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with methylene chloride. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over MgSO₄, and purified by column chromatography (methanol-ethyl acetate 20%) to provide the title compound.

30 Colorless oil. Yield 3.49 g (64%)

¹H-NMR (200 MHz, CDCl₃) δ: 1.07-1.96 (m, 4H), 2.24 (s, 3H), 2.37-2.47 (m, 4H), 2.62 (t, J=7.7 Hz, 2H), 3.74 (t, J=7.3 Hz, 2H), 7.12-7.33 (m, 5H), 7.66-7.77 (m, 2H), 7.79-7.88 (m, 2H).

35 4) Synthesis of 3-[N-methyl-N-(3-phenylpropan-1-yl)amino]propan-1-ylamine

To a solution of 3.49 (10.37 mM) of 3-[N-methyl-N-(3-phenylpropan-1-yl)amino]propan-1-ylphthalimide in ethanol (50 ml) was added 1.5 ml (30.92 mM) of hydrazine monohydrate at room temperature and the
5 mixture was refluxed for 40 minutes. The solid that formed was filtered off and the filtrate was concentrated. The residue was diluted with water, made strongly basic with sodium hydroxide, and, then, extracted with chloroform. The organic layer was
10 washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The solvent was then distilled off under reduced pressure to provide the title compound.

Colorless oil. Yield 2.09 g (98%)
15 ¹H-NMR (200 MHz, CDCl₃) δ: 1.55-1.87 (m, 4H), 2.22 (s, 3H), 2.34-2.43 (m, 4H), 2.59-2.67 (m, 2H), 2.75 (s, J=7.0 Hz, 2H), 7.13-7.36 (m, 5H).

Reference Example 32
Synthesis of 4-[(3-phenylpropan-1-yl)aminomethyl]-
20 piperidine

1) Synthesis of N-(3-phenylpropan-1-yl)-N-(1-tert-butoxycarbonylpiperidin-4-ylmethyl)trifluoroacetamide
Under nitrogen, 0.25 g (6.25 mM) of a 60% suspension of sodium hydride in liquid paraffin was
25 added to a solution of 1.73 g (5.57 mM) of N-(1-tert-butoxycarbonylpiperidin-4-ylmethyl)trifluoroacetoamide in N,N-dimethylformamide (20 ml) at 0°C and the mixture was stirred at 0°C for 30 minutes. To this mixture was added 1.0 ml (6.58 mM) of 1-bromo-3-phenylpropane and
30 the mixture was stirred at room temperature for 2.5 hours and further at 60°C for one hour. The reaction was stopped by adding water and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over MgSO₄, and purified by column chromatography (ethyl acetate-hexane 30%) to provide

the title compound.

Colorless liquid. Yield 1.49 g (62%)

¹H-NMR (200 MHz, CDCl₃) δ: 0.99-1.33 (m, 2H), 1.46 (s, 9H), 1.43-1.67 (m, 3H), 1.82-2.03 (m, 2H), 2.51-2.72 (m, 4H), 3.17-3.46 (m, 4H), 4.00-4.22 (m, 2H), 7.12-7.37 (m, 5H).

5 2) Synthesis of 4-[(3-phenylpropan-1-yl)aminomethyl]-piperidine

To a solution of 1.49 g (3.48 mM) of N-(3-phenyl-10 propan-1-yl)-N-[1-tert-butoxycarbonylpiperidin-4-ylmethyl]trifluoroacetamide in ethanol (10 ml) was added 1.0 ml (12 mM) of 12N-hydrochloric acid at room temperature and the mixture was stirred for 20 hours. The solvent was then distilled off under reduced pressure and 3 ml (36 mM) of 12N-hydrochloric acid was added to the residue. This mixture was stirred at room 15 temperature for 20 minutes. To this reaction mixture was added ethanol and the solvent was distilled off under reduced pressure to provide 1.29 g (quantitative) of a crude product as white solid. To a solution of 20 0.33 g (0.90 mM) of this crude product in ethanol (4 ml) was added 4 ml (4 mM) of 1N-aqueous solution of sodium hydroxide at room temperature and the mixture was stirred for 30 minutes. The ethanol was then 25 distilled off under reduced pressure and the residue was extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The solvent was then distilled off under reduced pressure to provide the 30 title compound.

Colorless liquid. Yield 0.1858 g (89%)

¹H-NMR (200 MHz, CDCl₃) δ: 0.96-1.24 (m, 2H), 1.45-4.92 (m, 5H), 2.46 (d, J=6.6 Hz, 2H), 2.50-2.72 (m, 6H), 2.98-3.16 (m, 2H), 7.10-7.33 (m, 5H).

35 Reference Example 33

Synthesis of ethyl 5-thia-1,8b-diazaacenaphthylene-4-

carboxylate

To a solution of ethyl (imidazo[1,2-a]pyridin-5-ylthio)acetate (11.8 g) in acetic acid (120 ml) was added hexamethylenetetramine (14.0 g) and the mixture
5 was reacted at 90°C for 10 hours. After this reaction mixture was allowed to cool, ethyl acetate (360 ml) was added and the mixture was washed with water. The organic layer was neutralized with 30% aqueous solution of sodium hydroxide under ice-cooling and washed again
10 with water. The organic layer was concentrated and n-hexane (100 ml) was added to the crystalline residue, followed by 1 hour of stirring at room temperature. The crystals were collected by filtration and dried to provide the title compound (9.6 g, 78%).

15 $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 1.30 (t, $J=7.1$ Hz, 3H), 4.22 (q, $J=7.1$ Hz, 2H), 5.70 (m, 1H), 6.55-6.64 (m, 2H), 6.80 (s, 1H), 7.01 (s, 1H).

Reference Example 34**Synthesis of 5-chloro-3-formylimidazo[1,2-a]pyridine**

20 A solution of 5-chloroimidazo[1,2-a]pyridine (997 mg) and hexamethylenetetramine (1.8 g) in acetic acid (10 ml) was stirred at 90°C for 5 hours. After the reaction mixture was allowed to cool, ethyl acetate-tetrahydrofuran (4/1; 200 ml) was added and the mixture
25 was washed with saturated aqueous solution of sodium chloride. The organic layer was neutralized with 2N-aqueous solution of sodium hydroxide, dried over MgSO_4 , and concentrated. The resulting crystals were rinsed with diethyl ether to provide the title compound (440 mg, 37%).

30 $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.20 (d, $J=7.4$ Hz, 1H), 7.44 (dd, $J=7.4$, 8.9 Hz, 1H), 7.76 (d, $J=8.9$ Hz, 1H), 8.50 (s, 1H), 10.71 (s, 1H).

Reference Example 35

35 **Synthesis of ethyl 5-thia-1,8b-diazaacenaphthylene-4-carboxylate**

A solution of imidazo[1,2-a]pyridine-5-thiol (448 mg), ethyl thioglycolate (0.36 ml), and sodium ethoxide (210 mg) in ethanol (10 ml) was refluxed with stirring for 3 hours. The mixture was then allowed to cool and 5 concentrated. The residue was diluted with ethyl acetate (10 ml) and extracted with 1N-hydrochloric acid. The aqueous layer was neutralized with 1N-NaOH/water and extracted with ethyl acetate, and the organic layer was washed with water and concentrated. 10 The resulting crystals were collected, rinsed with diisopropyl ether (20 ml), and dried to provide the title compound (430 mg, 65%).

Reference Example 36

Synthesis of 6-tert-butyldimethylsiloxy-2-(2-hydroxy-15 ethyl)-2,5,7,8-tetramethylchroman

1) Synthesis of methyl 6-hydroxy-2,5,7,8-tetramethylchroman-2-acetate

To a suspension of 10.0 g (37.83 mM) of 6-hydroxy-2,5,7,8-tetramethylchroman-2-acetic acid in methanol (50 ml) was added 0.5 ml (6 mM) of concentrated sulfuric acid at room temperature and the mixture was stirred for 3 days. To this reaction mixture was added a saturated aqueous solution of sodium hydrogen carbonate at 0°C until the pH had been brought to 5-7 20 and the solvent was then distilled off under reduced pressure. The residue was diluted with water and extracted with diethyl ether. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The solvent was then 25 distilled off under reduced pressure to provide the title compound as tan-colored oil.

Yield 7.69 g (75%)

¹H-NMR (CDCl₃) δ: 1.41 (s, 3H), 1.82-2.06 (m, 2H), 2.09 (s, 3H), 2.11 (s, 3H), 2.16 (s, 3H), 2.60-2.68 (m, 4H), 3.69 (s, 3H).

IR (neat): 3494, 2933, 1730, 1450, 1329, 1252, 1165,

1092, 1028, 924 cm⁻¹

2) Synthesis of methyl 6-tert-butyldimethylsiloxy-2,5,7,8-tetramethylchroman-2-acetate

Under nitrogen, 5.41 g (35.9 mM) of tert-butyldimethylsilyl chloride was added to a solution of 7.69 g (27.63 mM) of methyl 6-hydroxy-2,5,7,8-tetramethylchroman-2-acetate and 2.82 g (41.4 mM) of imidazole in DMF (54 ml) at room temperature and the mixture was stirred at 0°C for 20 hours. This reaction mixture was poured in saturated aqueous sodium hydrogen carbonate-diethyl ether under intense agitation to stop the reaction and, then, extracted with diethyl ether. The organic layer was washed with water and saturated aqueous solution of sodium chloride and dried over MgSO₄. The resulting crude product was purified by column chromatography (ethyl acetate-hexane: 10%) to provide the title compound as yellow oil.

Yield 11.35 g (quant.)

¹H-NMR (CDCl₃) δ: 0.11 (s, 6H), 1.04 (s, 9H), 1.41 (s, 3H), 1.85-2.03 (m, 2H), 2.05 (s, 6H), 2.09 (s, 3H), 2.55-2.64 (m, 4H), 3.69 (s, 3H).

IR (neat): 2937, 2858, 1740, 1460, 1254, 1092, 941, 887, 837, 779 cm⁻¹.

3) Synthesis of 6-tert-butyldimethylsiloxy-2-(2-hydroxyethyl)-2,5,7,8-tetramethylchroman

Under nitrogen, a solution of 11.35 g (28.91 mM) of methyl 6-tert-butyldimethylsiloxy-2,5,7,8-tetramethylchroman-2-acetate in diethyl ether (10 ml) was added to a suspension of 1.1 g (28.99 mM) of lithium aluminum hydride in diethyl ether (50 ml) at 0°C and the mixture was stirred at the prevailing temperature for one hour. Then, water (1.1 ml), 15% aqueous solution of NaOH (1.1 ml), and water (1.1 ml) were added in that order and the mixture was stirred at room temperature for 30 minutes. To this mixture was added magnesium sulfate, and after the precipitate was

filtered off, the solvent was distilled off under reduced pressure to provide a crude product. This crude product was purified by column chromatography (ethyl acetate-hexane: 20-30%) to provide the title
5 compound as light-yellow oil (9.65 g, 92%).

¹H-NMR (CDCl₃) δ: 0.12 (s, 6H), 1.05 (s, 9H), 1.28 (s, 3H), 1.70-2.02 (m, 4H), 2.06 (s, 6H), 2.10 (s, 3H), 2.50-2.67 (m, 2H), 3.83-4.03 (m, 2H).

Reference Example 37

10 Synthesis of 1-(trans-4-aminomethyl-1-cyclohexylmethyl)-4-phenylpiperidine dihydrochloride 1)
Synthesis of trans-4-[N-(tert-butoxycarbonyl)amino-methyl]cyclohexane-1-carboxylic acid

To a suspension of 47.16 g (300 mM) of trans-4-aminomethylcyclohexane-1-carboxylic acid in purified water (300 ml)-THF (300 ml) was added 41.8 ml (300 mM) of triethylamine as well as 65.48 g (300 mM) of di-tert-butyl dicarbonate and the mixture was stirred at room temperature for 2 hours. Then, 12N-hydrochloric
15 acid was added until the aqueous layer had been brought to pH 2 and the mixture was then extracted with 200 ml of ethyl acetate. The organic layer was washed with 300 ml of saturated aqueous solution of sodium chloride and dried over MgSO₄, and the solvent was distilled off
20 under reduced pressure to provide 67.3 g (yield 87.2%) of crude product as white solid. This crude product was not purified but used as it was in the next reaction.

¹H-NMR (200 MHz, DMSO-d₆) δ: 0.74-0.98 (m, 2H), 1.09-1.47 (m, 12H), 1.61-1.79 (m, 2H), 1.79-1.98 (m, 2H), 1.98-2.19 (m, 1H), 2.76 (t, 2H, J=6.2 Hz), 6.78 (t, 1H, J=5.4 Hz).

IR (KBr): 3375, 1694, 1529 cm⁻¹.

2) Synthesis of trans-4-[N-(tert-butoxycarbonyl)amino-methyl]cyclohexane-1-methanol

To 400 ml of 1.0M borane-THF was added 51.7 g (200

mM) of trans-4-[N-(tert-butoxycarbonyl)aminomethyl]cyclohexane-1-carboxylic acid in small portions at 0°C and the mixture was stirred at room temperature for 2 hours. This reaction mixture was then poured in iced water and, after thorough stirring, extracted with 200 ml of ethyl acetate. The organic layer was washed with 250 ml of saturated aqueous solution of sodium chloride and dried over MgSO₄ and the solvent was distilled off under reduced pressure to provide 47.06 g (yield 96.7%) of crude product as white solid. This crude product was not purified but used as it was in the next reaction.

¹H-NMR (200 MHz, DMSO-d₆) δ: 0.74-0.96 (m, 4H), 1.14-1.45 (m, 11H), 1.62-1.81 (m, 4H), 2.76 (t, 2H, J=6.2 Hz), 3.20 (t, 2H, J=6.0 Hz), 4.31 (t, 1H, OH, J=6.0 Hz), 6.72 (t, 1H, J=5.4 Hz).

IR (KBr): 3376, 1698, 1533 cm⁻¹.

3) Synthesis of N-(trans-4-bromomethyl-1-cyclohexylmethyl)-N-(tert-butoxycarbonyl)amine

To a solution of 5.00 g (20.55 mM) of trans-4-[N-(tert-butoxycarbonyl)aminomethyl]cyclohexane-1-methanol and 6.42 g (24.48 mM) of triphenylphosphine in methylene chloride (30 ml) was added 13.63 g (41.1 mM) of carbon tetrabromide at 0°C and the mixture was stirred at room temperature for 20 hours. This reaction mixture was purified by column chromatography (ethyl acetate-hexane: 10%) to provide the title compound as white solid.

Yield 2.53 g (40%)

¹H-NMR (200 MHz, CDCl₃) δ: 0.83-1.14 (m, 4H), 1.44 (s, 9H), 1.49-1.70 (m, 2H), 1.71-2.01 (m, 4H), 2.98 (t, J=6.4 Hz, 2H), 3.28 (d, J=6.2 Hz, 2H), 4.47-4.66 (m, 1H).

IR (KBr): 3390, 2921, 1685, 1524, 1257, 1174, 613 cm⁻¹.

4) Synthesis of 1-[trans-4-[N-(tert-butoxycarbonyl)aminomethyl]-1-cyclohexylmethyl]-4-

phenylpiperidine

A solution of 2.51 g (8.20 mM) of N-(trans-4-bromomethyl-1-cyclohexylmethyl)-N-(tert-butoxycarbonyl)amine, 1.32 g (8.19 mM) of 4-phenylpiperidine, and 2.3 ml (16.5 mM) of triethylamine in ethanol (10 ml) was refluxed under nitrogen for 64 hours. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. This crude product was purified by column chromatography (methanol-ethyl acetate: 10%) to provide the title compound as light-yellow solid.

Yield 1.02 g (32%)

15 ¹H-NMR (200 MHz, CDCl₃) δ: 0.85-0.99 (m, 4H), 1.45 (s, 9H), 1.61-2.15 (m, 12H), 2.22 (d, J=6.8 Hz, 2H), 2.39-2.56 (m, 1H), 2.90-3.10 (m, 4H), 4.51-4.64 (m, 1H), 7.13-7.39 (m, 5H).

20 IR (KBr): 3386, 2937, 1691, 1522, 1443, 1279, 1250, 1171, 698 cm⁻¹.

5) Synthesis of 1-(trans-4-aminomethyl-1-cyclohexylmethyl)-4-phenylpiperidine dihydrochloride

To a solution of 1.02 g (2.64 mM) of 1-[trans-4-(N-(tert-butoxycarbonyl)aminomethyl)-1-cyclohexylmethyl]-4-phenylpiperidine in ethanol (10 ml) was added 10 ml (120 mM) of 12N-hydrochloric acid at room temperature and the mixture was stirred for one hour. This reaction mixture was concentrated under reduced pressure (crystals separated out) and diethyl ether was added to the residue. The resulting crystal crop was harvested by filtration and rinsed with ethanol and diethyl ether to provide the title compound as light-purple crystals.

Yield 0.81 g (85%)

35 ¹H-NMR (200 MHz, DMSO-d₆) δ: 0.85-1.11 (m, 4H), 1.68-2.08 (m, 6H), 2.14-2.40 (m, 2H), 2.55-3.17 (m,

7H), 3.40-3.64 (m, 4H), 7.18-7.41 (m, 5H), 7.92-8.16 (m, 3H), 10.17-10.44 (m, 1H).

IR (neat): 1603, 1504, 1433, 9985, 945, 754, 702 cm⁻¹.

Reference Example 38

5 Synthesis of 1-[4-(aminomethyl)benzyl]-4-phenylpiperidine dihydrochloride

1) Synthesis of 4-[N-(tert-butoxycarbonyl)aminomethyl]-benzoic acid

To a suspension of 15 g (99.2 mM) of 4-(aminomethyl)benzoic acid in THF (100 ml) was added 100 ml (100 mM) of 1N-aqueous solution of NaOH at room temperature, followed by addition of 23.8 g (109 mM) of di-tert-butyl dicarbonate, and the mixture was stirred for 20 hours. To this reaction mixture was added 6N-hydrochloric acid so as to bring the pH to 4 and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The solvent was distilled off under reduced pressure and hexane was added to the crystalline residue. The crystals were collected by filtration and rinsed with hexane to provide the title compound as white crystals.

Yield 22.23 g (89%)

m.p. 161-162°C

25 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40 (9H, s), 4.19 (2H, d, J=6.4 Hz), 7.34 (2H, d, J=8.2 Hz), 7.39-7.50 (1H, m), 7.89 (2H, d, J=8.2 Hz).

IR (KBr): 3357, 2982, 1686, 1510, 1431, 1292, 1246, 1171 cm⁻¹.

30 2) Synthesis of 4-[N-(tert-butoxycarbonyl)aminomethyl]-1-phenylmethanol

To 100 ml (100 mM) of 1M borane-THF complex was added 25.13 g (100 mM) of 4-[N-(tert-butoxycarbonyl)aminomethyl]benzoic acid at 0°C and the mixture was stirred at room temperature for 1.5 hours. The reaction was stopped by adding iced water and the

reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The solvent was then distilled off under reduced pressure
5 and the resulting crystal crop was harvested by filtration and rinsed with hexane to provide the title compound as white crystals.

Yield 11.07 g (47%)

m.p. 88-90°C

10 ¹H-NMR (200 MHz, CDCl₃) δ: 1.46 (9H, s), 4.31 (2H, d, J=6.0 Hz), 4.68 (2H, s), 4.76-5.06 (1H, s), 7.23-7.38 (m, 4H).

IR (KBr): 3347, 2980, 1686, 1514, 1248, 1171 cm⁻¹.

15 3) Synthesis of 1-[4-[N-(tert-butoxycarbonyl)aminomethyl]benzyl]-4-phenylpiperidine

To a solution of 5.0 g (21.07 mM) of 4-[N-(tert-butoxycarbonyl)aminomethyl]-1-phenylmethanol and 5.9 ml (42.33 mM) of triethylamine in THF (42 ml) was added 2.5 ml (32.3 mM) of methanesulfonyl chloride at 0°C and the mixture was stirred at the prevailing temperature for one hour. The reaction was then stopped by adding saturated aqueous solution of sodium hydrogen carbonate and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous solution of sodium chloride and dried over MgSO₄. The solvent was then distilled off under reduced pressure to provide 6.72 g (21.07 mM) of crude product as light-brown solid. To a solution of 6.72 g (21.07 mM) of this crude mesylate in ethanol (42 ml) was added 5.9 ml (42.33 mM) of triethylamine as well as 3.40 g (21.09 mM) of 4-phenylpiperidine and the mixture was refluxed for 18 hours. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous solution of sodium chloride and dried over magnesium

sulfate. After concentration, the crude product was purified by column chromatography (ethyl acetate-hexane: 50%) to provide the title compound as light-yellow solid.

5 Yield 5.77 g (72%)

m.p. 73-74°C

¹H-NMR (200 MHz, CDCl₃) δ: 1.46 (9H, s), 1.73-1.88 (4H, m), 1.99-2.19 (1H, m), 2.94-3.08 (2H, m), 3.54 (2H, s), 4.31 (2H, d, J=5.8 Hz), 4.73-4.96 (1H, m), 7.13-7.36 (4H, m).

10 IR (KBr): 3389, 1690, 1518, 1269, 1171 cm⁻¹.

4) Synthesis of 1-[4-(aminomethyl)benzyl]-4-phenyl-piperidine dihydrochloride

To 5.77 g (15.16 mM) of 1-[4-[N-(tert-butoxy-carbonyl)aminomethyl]benzyl]-4-phenylpiperidine was added 10 ml (120 mM) of 12N-hydrochloric acid at room temperature and the mixture was stirred at the prevailing temperature for 2 hours. To this reaction mixture was added ethanol and the mixture was concentrated under reduced pressure. To the residue were added ethanol and diethyl ether and the resulting crystals were harvested by filtration. This crystal crop was rinsed with ethanol and diethyl ether to provide the title compound as white crystals.

25 Yield 4.72 g (88%)

m.p. 257-260°C (dec.)

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.82-2.01 (2H, m), 2.05-2.32 (2H, m), 2.68-2.88 (1H, m), 2.91-3.15 (2H, m), 3.28-3.56 (2H, m), 3.99-4.12 (2H, m), 4.32 (2H, d, J=5.0 Hz), 7.12-7.44 (5H, m), 7.59 (2H, d, J=8.0 Hz), 7.73 (2H, d, J=8.0 Hz), 8.34-8.74 (3H, m), 11.25-11.50 (1H, m).

IR (KBr): 2091, 1601, 1530, 1450, 1533, 1422, 1399, 939, 746, 700 cm⁻¹.

35 Reference Example 39

Synthesis of 1-[4-(aminomethyl)benzyl]-4-

benzylpiperidine dihydrochloride**1) Synthesis of 1-[4-[N-(tert-**
butoxycarbonyl)aminomethyl]benzyl]-4-benzylpiperidine

To a solution of 5.0 g (21.07 mM) of 4-[N-(tert-butoxycarbonyl)aminomethyl]-1-phenylmethanol and 5.9 ml (42.33 mM) of triethylamine in THF (42 ml) was added 2.5 ml (32.3 mM) of methanesulfonyl chloride at 0°C and the mixture was stirred at the prevailing temperature for one hour. The reaction was stopped by adding 10 saturated aqueous solution of sodium hydrogen carbonate and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous solution of sodium chloride and dried over MgSO₄. The solvent was then distilled off under 15 reduced pressure to provide 7.21 g (21.07 mM) of crude product as light-brown solid. To a solution of 7.21 g (21.07 mM) of this crude mesylate in ethanol (42 ml) was added 5.9 g (42.33 mM) of triethylamine as well as 3.69 g (21.05 mM) of 4-phenylpiperidine and the mixture 20 was refluxed for 18 hours. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous solution of sodium chloride and dried over MgSO₄.

25 After concentration, the crude product was purified by column chromatography (ethyl acetate-hexane: 50%) to provide the title compound as light-yellow oil.

Yield 5.77 g (69%)

¹H-NMR (200 MHz, CDCl₃) δ: 1.20-1.40 (2H, m), 1.46 (9H, s), 1.85-2.01 (2H, m), 2.53 (2H, d, J=6.2 Hz), 2.78-2.93 (2H, m), 3.48 (2H, s), 4.29 (2H, d, J=6.0 Hz), 4.70-4.88 (1H, m), 7.07-7.34 (9H, m).

IR (neat): 3350, 2924, 1709, 1508, 1452, 1365, 1252, 1173 cm⁻¹.

35 **2) Synthesis of 1-[4-(aminomethyl)benzyl]-4-benzyl-piperidine dihydrochloride**

To 5.77 g (14.6 mM) of 1-[4-(*N*-(tert-butoxycarbonyl)aminomethyl]benzyl)-4-benzylpiperidine was added 10 ml (120 mM) of 12N-hydrochloric acid at room temperature and the mixture was stirred at the prevailing temperature for one hour. After addition of ethanol, the mixture was concentrated under reduced pressure and ethanol and diethyl ether were added to the residue. The resulting crystal crop was harvested by filtration and rinsed with ethanol and diethyl ether to provide the title compound as white crystals.

Yield 4.25 g (79%)

m.p. 245-250°C

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.50-1.88 (5H, m), 2.65-2.98 (2H, m), 3.16-3.41 (4H, m), 3.98-4.14 (2H, m), 4.17-4.28 (2H, m), 7.12-7.36 (5H, m), 7.55 (2H, d, J=8.4 Hz), 7.65 (2H, d, J=8.4 Hz), 8.29-8.62 (3H, m), 10.70-10.98 (1H, m).
IR (KBr): 3395, 2980, 2500, 1593, 1512, 1454, 1078, 881, 860, 748, 700 cm⁻¹.

20 Reference Example 40

Synthesis of *tert*-butyl 4-

[(dimethoxyphosphoryl)acetyl]piperidine-1-carboxylate

1) Synthesis of ethyl 1-(*tert*-

butoxycarbonyl)piperidine-4-carboxylate

To a solution of 16.377 g (104.17 mM) of ethyl piperidine-4-carboxylate in 150 ml of tetrahydrofuran was added a solution of 25.0 g (115 mM) of di-*tert*-butyl dicarbonate in 50 ml of tetrahydrofuran dropwise at room temperature and the mixture was stirred at the prevailing temperature for 3 hours. The solvent was then distilled off under reduced pressure and the residue was purified by silica gel column chromatography (hexane-ethyl acetate : 9/1 to 6/1) to provide the title compound.

35 Colorless liquid. Yield 26.631 g (99%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.258 (3H, t, 7.1 Hz), 1.456

(9H, s), 1.518-1.718 (2H, m), 1.880 (2H, br d, 13.3 Hz), 2.434 (1H, tt, 4.0 Hz, 11.0 Hz), 2.832 (2H, br t, 13.9 Hz), 4.031 (2H, br d, 13.4 Hz), 4.145 (2H, q, 7.1 Hz).

5 IR (neat): 2976, 1732, 1695, 1421, 1367, 1313, 1240, 1167, 1041 cm⁻¹.

2) Synthesis of tert-butyl 4-[(dimethoxyphosphoryl)-acetyl]piperidine-1-carboxylate

To a solution of 10.1 g (81.3 mM) of dimethyl methylphosphonate in 100 ml of tetrahydrofuran was added 53.2 ml (85.2 mM) of 1.6M n-butyllithium-hexane dropwise at -78°C and the mixture was stirred at the prevailing temperature for 10 minutes. To this mixture was added a solution of 9.964 g (38.721 mM) of ethyl 1-(tert-butoxycarbonyl)piperidine-4-carboxylate in 50 ml of tetrahydrofuran at -78°C and the mixture was stirred until the temperature had recovered to room temperature. This reaction mixture was poured in aqueous solution of ammonium chloride and extracted with 3 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate : 1/1 to ethyl acetate) to provide the title compound.

20 Colorless liquid. Yield 11.487 g (88%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.453 (9H, s), 1.299-1.700 (2H, m), 1.865 (2H, br d, 11.0 Hz), 2.661-2.850 (3H, m), 3.147 (2H, d, 22.8 Hz), 3.793 (6H, d, 11.4 Hz), 4.109 (2H, br d, 12.8 Hz).

25 IR (neat): 3475, 2931, 1691, 1423, 1242, 1169, 1030, 810 cm⁻¹.

Reference Example 41

Synthesis of tert-butyl 4-[(4-(dimethoxyphosphoryl)-3-oxobutyl)piperidine-1-carboxylate

35 1) Synthesis of tert-butyl (E)-4-(2-

ethoxycarbonylvinyl)piperidine-1-carboxylate

To a solution of 10.7 g (84.4 mM) of oxalyl chloride in 100 ml of tetrahydrofuran was added 12.0 ml (169 mM) of dimethyl sulfoxide dropwise at -78°C and
5 the mixture was stirred for 5 minutes. Then, a solution of []g (mM) of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate in 100 ml of tetrahydrofuran was added dropwise and the mixture was stirred at -78°C for 15 minutes. To this mixture was
10 added 47.0 ml (338 mM) of triethylamine at -78°C and the temperature was increased to room temperature. This reaction mixture was poured in water and extracted with 3 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄ and the solvent was
15 distilled off under reduced pressure. The resulting crude tert-butyl 4-formylpiperidine-1-carboxylate was not purified but used as it was in the next reaction.

A 60% suspension of sodium hydride in liquid paraffin, 2.48 g (61.9 mM), was washed with hexane
20 twice and suspended in 50 ml of toluene. Then, under ice-cooling, a solution of 15.1 g (67.5 mM) of ethyl diethylphosphonoacetate in 50 ml of toluene was added dropwise and the mixture was stirred at room temperature for 30 minutes. To this mixture was
25 further added a solution of the crude-tert-butyl 4-formylpiperidine-1-carboxylate obtained above in 100 ml of toluene dropwise at room temperature and the mixture was stirred at room temperature overnight. (The stirring had to be discontinued after about 1 hour
30 because of formation of a gum-like precipitate). This reaction mixture was poured in water and extracted with 2 portions of diethyl ether. The organic layers were pooled and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The crude
35 product thus obtained was purified by silica gel column chromatography (hexane-ethyl acetate : 6/1) to provide

the title compound.

Yellow liquid. Yield 14.281 g (90%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.236-1.420 (2H, m), 1.293
5 (3H, t, 7.0 Hz), 1.460 (9H, s), 1.737 (2H, br d,
13.8 Hz), 2.205-2.383 (1H, m), 2.762 (2H, br t,
11.9 Hz), 4.121 (2H, br d, 12.4 Hz), 4.193 (2H, q,
7.1 Hz), 5.801 (1H, dd, 1.2 Hz, 16.0 Hz), 6.897
(1H, dd, 6.6 Hz, 15.8 Hz).

IR (neat): 2978, 1718, 1693, 1421, 1275, 1169 cm⁻¹.

10 2) Synthesis of tert-butyl (E)-4-[4-(dimethoxyphosphoryl)-3-oxo-1-butenyl]piperidine-1-carboxylate

To a solution of 13.1 g (106 mM) of dimethyl
15 methylphosphonate in 100 ml of tetrahydrofuran was
added 69.2 ml (111 mM) of 1.6M n-butyllithium-hexane
dropwise at -78°C and the mixture was stirred at the
prevailing temperature for 10 minutes. To this
reaction mixture was added a solution of 14.271 g
(50.362 mM) of tert-butyl (E)-4-(2-
20 ethoxycarbonylvinyl)piperidine-1-carboxylate in 100 ml
of tetrahydrofuran at -78°C and the mixture was stirred
until the temperature had recovered to room
temperature. This reaction mixture was poured in
aqueous solution of ammonium chloride and extracted
25 with 3 portions of ethyl acetate. The organic layers
were pooled and dried over MgSO₄ and the solvent was
distilled off under reduced pressure. The residue was
purified by silica gel column chromatography (hexane-
ethyl acetate : 1/1 to ethyl acetate) to provide the
30 title compound.

Yellow liquid. Yield 11.768 g (65%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.115-1.403 (2H, m), 1.462
(9H, s), 1.559-1.832 (2H, m), 2.271-2.394 (1H, m),
2.769 (2H, br t, 12.1 Hz), 3.228 (2H, d, 22.6 Hz),
35 3.786 (6H, d, 11.4 Hz), 3.962-4.189 (2H, m), 6.212
(1H, dd, 1.3 Hz, 15.9 Hz), 6.862 (1H, dd, 6.5 Hz,

15.7 Hz).

IR (neat): 3479, 2958, 1689, 1425, 1250, 1171, 1032, 970, 814 cm⁻¹.

3) Synthesis of tert-butyl 4-[4-(dimethoxyphosphoryl)-
5 3-oxobutyl]piperidine-1-carboxylate

A solution of 5.443 g (15.062 mM) of tert-butyl (E)-4-[4-(dimethoxyphosphoryl)-3-oxo-1-butenyl]piperidine-1-carboxylate in 50 ml of methanol was subjected to hydrogenation using 3 g of 10% palladium-on-carbon (50% hydrous) as a catalyst at room temperature and atmospheric pressure until the starting material had been no longer detected. The catalyst was removed by filtration with the aid of celite and the catalyst was washed with methanol. The filtrate and washes were pooled and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate : 1/1 to ethyl acetate) to provide the title compound.

20 Colorless liquid. Yield 4.732 g (87%)

¹H-NMR (CDCl₃, 200 MHz) δ: 0.994-1.691 (9H, m), 1.449 (9H, s), 2.659 (2H, br t, 12.1 Hz), 3.094 (2H, d, 22.6 Hz), 3.789 (6H, d, 11.4 Hz), 3.962-4.185 (2H, m).

25 IR (neat): 3479, 2927, 1689, 1423, 1246, 1167, 1030, 812 cm⁻¹.

Reference Example 42
Synthesis of tert-butyl 4-(diethoxyphosphorylmethylthiomethyl)piperidine-1-
30 carboxylate

1) Synthesis of S-(diethoxyphosphorylmethyl)thioacetate

To a solution of 17.527 g (93.938 mM) of diethyl chloromethylphosphonate in 50 ml of N,N-dimethylformamide was added 12.9 g (113 mM) of potassium thioacetate and the mixture was stirred at

100°C for 3 hours. This reaction mixture was poured in water, saturated with sodium chloride, and extracted with 4 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄, and the solvent was
5 distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate : 3/1 to 1/1) to provide the title compound.

Orange-colored liquid. Yield 13.059 g (61%)
10 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.330 (6H, t, 7.2 Hz), 2.398 (3H, s), 3.231 (2H, d, 14.0 Hz), 4.141 (4H, quint, 7.4 Hz).

IR (neat): 2983, 1701, 1252, 1051, 1024, 968, 623 cm⁻¹.

2) Synthesis of tert-butyl 4-(diethoxyphosphorylmethyl-thiomethyl)piperidine-1-carboxylate
15

To a solution of 1.529 g (6.759 mM) of S-(diethoxyphosphorylmethyl) thioacetate in 30 ml of methanol was added 1.30 g (6.76 mM) of 28% sodium methoxide-methanol under ice-cooling and the mixture
20 was stirred at the prevailing temperature for 20 minutes. To this reaction mixture was added crude tert-butyl 4-(mesyloxymethyl)piperidine-1-carboxylate [which was prepared by adding 0.73 ml (9.46 mM) of methanesulfonyl chloride to a solution of 1.75 g (8.11 mM) of tert-butyl 4-(hydroxymethyl-thiomethyl)piperidine-1-carboxylate and 1.51 ml (10.8 mM) of triethylamine in 30 ml of tetrahydrofuran with ice-cooling, stirring the mixture at the prevailing temperature for 0.5 hour, pouring the mixture in water, extracting it with 2 portions of ethyl acetate, drying the pooled organic layer over MgSO₄, and concentrating it], and the mixture was refluxed for 3 hours. The solvent was distilled off under reduced pressure and the residue was diluted with water and extracted with 2 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄, and the solvent was

distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate: 3/1 to ethyl acetate) to provide the title compound.

5 Yellow liquid. Yield 2.325 g (90%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.042-1.256 (2H, m), 1.353 (6H, t, 6.9 Hz), 1.454 (9H, s), 1.552-1.730 (1H, m), 1.804 (2H, br d, 13.8 Hz), 2.629-2.778 (6H, m), 4.060-4.130 (2H, m), 4.181 (4H, quint, 7.4

10 Hz).

IR (neat): 2978, 2929, 1691, 1423, 1246, 1163, 1053, 1026, 966, 827 cm⁻¹.

Reference Example 43

Synthesis of tert-butyl 4-(diethoxyphosphorylmethane-sulfonylmethyl)piperidine-1-carboxylate

A solution of 2.325 g (6.095 mM) of tert-butyl 4-(diethoxyphosphorylmethylthiomethyl)piperidine-1-carboxylate, 2.76 g (24.4 mM) of 30% aqueous solution of hydrogen peroxide, and 0.2 g of sodium tungstate in 50 ml of methanol was stirred at room temperature overnight. This reaction mixture was poured in water and extracted with 4 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate : 1/1 to ethyl acetate) to provide the title compound.

Colorless liquid. Yield 2.041 g (81%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.224-1.410 (2H, m), 1.376 (6H, t, 7.1 Hz), 1.452 (9H, s), 1.943 (2H, br d, 13.2 Hz), 2.203-2.335 (1H, m), 2.768 (2H, br t, 12.3 Hz), 3.325 (2H, d, 6.6 Hz), 3.567 (2H, d, 16.4 Hz), 4.090 (2H, br d, 12.4 Hz), 4.234 (4H, qd, 7.1 Hz, 8.3 Hz).

35 IR (neat): 2976, 1689, 1425, 1311, 1250, 1165, 1051, 1022, 972, 835, 798 cm⁻¹.

Reference Example 44

Synthesis of tert-butyl 4-(diphenoxypyrophosphorylmethane-sulfonylaminomethyl)piperidine-1-carboxylate

A solution of 2.405 g (5.947 mM) of phenyl diphenoxypyrophosphorylmethanesulfonate and 1.66 g (7.73 mM) of 1-(tert-butoxycarbonyl)piperidine-4-ylmethylamine in 50 ml of toluene was refluxed overnight. The solvent was then distilled off under reduced pressure and the residue was purified by silica gel column chromatography (hexane-ethyl acetate : 2/1 to 1/1) to provide the title compound.

Yellow liquid. Yield 2.245 g (72%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.000-1.181 (2H, m), 1.449 (9H, s), 1.524-1.724 (3H, m), 2.636 (2H, t, 13.0 Hz), 2.973 (2H, t, 6.4 Hz), 3.883 (2H, d, 16.0 Hz), 4.087 (2H, br d, 11.0 Hz), 5.409 (1H, t, 6.4 Hz), 7.186-7.264 (6H, m), 7.332-7.405 (4H, m). IR (neat): 3207, 2934, 1687, 1489, 1425, 1338, 1277, 1213, 1182, 1163, 951, 766 cm⁻¹.

Reference Example 45

Synthesis of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid

To a solution of 3.00 g (12.18 mM) of ethyl 5-thia-1,8b-diazaacenaphthylene-4-carboxylate in methanol (9 ml) was added 18 ml (18 mM) of 1N-aqueous solution of sodium hydroxide at room temperature and the mixture was stirred for 2.5 hours. This reaction mixture was cooled to 0°C and 1N-hydrochloric acid was added until the pH had been brought to 5. The resulting crystals were harvested by filtration. This crystal crop was rinsed with water, ethanol and diethyl ether to provide the title compound as orange-colored solid (yield 1.98 g, 69%).

Elemental analysis for C₁₀H₆N₂O₂S•1.0H₂O

Calcd.: C, 50.84; H, 3.41; N, 11.86

Found : C, 50.59; H, 3.41; N, 11.62

Reference Example 46

Synthesis of 1-aminoacetyl-4-(3-phenylpropan-1-yl)piperazine dihydrochloride

5 1) Synthesis of tert-butyl 4-(3-phenylpropyl)piperazine-1-carboxylate

To a solution of 7.06 g (37.9 mmol.) of 1-tert-butoxycarbonylpiperazine in ethanol (50 ml) were added, at room temperature, 8.0 ml (57.4mmol.) of triethylamine and 7.09 g (39.7 mmol.) of 1-bromo-3-phenylpropane. The mixture was heated under reflux for 16 hours under nitrogen atmosphere. To the reaction system was added ethyl acetate. The mixture was washed with water and a saturated aqueous saline solution, which was dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by means of a column chromatography (ethyl acetate/hexane=25-50%). The solvent was distilled off under reduced pressure to give the object compound as a pale yellow liquid product. The yield was 8.69 g (75%).

¹H-NMR (CDCl₃, 200 MHz) δ: 1.46 (9H, s), 1.75-1.90 (2H, m), 2.30-2.42 (6H, m), 2.64 (2H, t, J=7.6 Hz), 3.43 (4H, t, J=5.2 Hz), 7.11-7.30 (5H, m).

IR (neat): 1699, 1456, 1419, 1365, 1288, 1238, 1173, 25 1126, 1007, 866, 748, 700 cm⁻¹.

2) Synthesis of 1-(3-phenylpropyl)-piperazine dihydrochloride

To 8.45 g (27.8 mmol.) of tert-butyl 4-phenylpropylpiperazine-1-carboxylate was added, at room temperature, 10 ml (120 mmol.) of 12N hydrochloric acid. The mixture was stirred for one hour. To the reaction system was added ethanol, which was then concentrated under reduced pressure. To the resulting white crystalline precipitate was added diethyl ether, which was subjected to filtration to collect the crystals. The crystals were washed with ethanol and

diethyl ether to give the object compound as white crystals. Further, from the filtrate, crystallization was conducted to give the object compound as white crystals.

5 Yield: first crop 5.41 g (70%)
second crop 1.77 g (23%)

m.p.182-189°C

¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.91-2.13 (2H, m), 2.65 (2H, t, J=7.8 Hz), 3.02-3.86 (10H, m), 7.15-7.37

10 (5H, m), 9.46-9.96 (2H, m).

IR (KBr): 3500, 3410, 3026, 2939, 2403, 1554, 1443, 1385, 966, 762, 706 cm⁻¹.

3) Synthesis of 1-[N-(tert-butoxycarbonyl)aminoacetyl]-4-(3-phenylpropan-1-yl)piperazine

15 To a suspension of 1.90 g (10.8 mmol.) of N-tert-butoxycarbonylglycine and 2.48 g (16.2 mmol.) of 1-hydroxybenzotriazole monohydrate in acetonitrile (20 ml) was added, at room temperature, 3.11 g (16.2 mmol.) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride. The mixture was stirred for one hour. To the reaction system was added a solution of 3.00 g (10.8 mmol.) of 1-(3-phenylpropyl)-piperazine dihydrochloride, 3.29 g (21.6 mmol.) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1.5 ml (10.8 mmol.) of triethylamine in acetonitrile (15 ml). The mixture was stirred for further one hour. The solvent was distilled off under reduced pressure. To the residue were added water and ethyl acetate, which was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous saline solution, followed by drying over magnesium sulfate. The solvent was distilled off under reduced pressure to leave a crude product, which was purified by means of a column chromatography (ethyl acetate - methanol/ethyl acetate 10%). The solvent was

distilled off under reduced pressure to give the object compound as a pale yellow oily product. The yield was 3.63 g (93%).

¹H-NMR (CDCl₃, 200 MHz) δ: 1.45 (9H, s), 1.73-1.90 (2H, m), 2.30-2.48 (6H, m), 2.65 (2H, t, J=7.6 Hz), 3.32-3.43 (2H, m), 3.59-3.69 (2H, m), 3.95 (2H, d, J=4.4 Hz), 5.46-5.58 (1H, m), 7.12-7.34 (5H, m).
IR (KBr): 3417, 2937, 1713, 1655, 1462, 1242, 1171, 1026, 752, 702 cm⁻¹.

10 4) Synthesis of 1-aminoacetyl-4-(3-phenylpropan-1-yl)piperazine dihydrochloride

To 3.48 g (9.63 mmol.) of 1-[N-(tert-butoxycarbonyl)aminoacetyl]-4-(3-phenylpropan-1-yl)piperazine was added, at room temperature, 7 ml (84 mmol.) of 12N hydrochloric acid. The mixture was stirred for 30 minutes. To the reaction system was added ethanol to allow crystals to precipitate. The reaction mixture was concentrated under reduced pressure, to which were added diethyl ether and ethanol. The crystals were collected by filtration and washed with diethyl ether to give the object compound as white crystals. The yield was 2.81 g (87%).

m.p. 223-227°C (decomp.)

¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.97-2.20 (2H, m), 2.65 (2H, t, J=7.8 Hz), 2.79-3.74 (8H, m), 3.78-4.09 (3H, m), 4.32-4.51 (1H, m), 7.15-7.38 (5H, m), 8.12-8.49 (3H, m), 11.61-11.84 (1H, m).

IR (KBr): 3423, 3361, 2995, 2931, 2559, 2465, 1670, 1498 cm⁻¹.

30 Reference Example 47

Synthesis of 1-Aminoacetyl-4-(2-phenethyl)piperazine dihydrochloride

1) Synthesis of tert-butyl 4-(2-phenethyl)piperazine-1-carboxylate

35 To a solution of 7.00 g (37.6 mmol.) of 1-tert-butoxycarbonylpiperazine in ethanol (50 ml) were added,

at room temperature, 8.0 ml (57.4 mmol.) of triethylamine and 8.42 g (45.4 mmol.) of phenethyl bromide. The mixture was heated under reflux for 16 hours under nitrogen atmosphere. To the reaction system were further added 2 ml (14.3 mmol.) of triethylamine and 2 ml (14.6 mmol.) of phenethyl bromide. The mixture was heated for further four hours under reflux. To the reaction system was added ethyl acetate, which was washed with water and a saturated aqueous saline solution, followed by drying over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by means of a column chromatography (ethyl acetate/hexane 30-50%), followed by distilling off the solvent to give the object compound as a white crystalline product. The yield was 8.03 g (74%). m.p. 62-65°C
¹H-NMR (CDCl₃, 200 MHz) δ: 1.47 (9H, s), 2.44-2.49 (4H, m), 2.55-2.66 (2H, m), 2.74-2.88 (2H, m), 3.44-3.49 (2H, m), 7.15-7.36 (5H, m).
IR (KBr): 2976, 2868, 2818, 1687, 1414, 1252, 1174, 1120, 1001, 711, 735, 696 cm⁻¹.
2) Synthesis of 1-(2-phenethyl)piperazine dihydrochloride
To 7.94 g (27.34 mmol.) of tert-butyl 4-(2-phenethyl)piperazine-1-carboxylate was added, at room temperature, 10 ml (120 mmol.) of 12N hydrochloric acid. The mixture was stirred for 30 minutes. To the reaction system was added ethanol. To the resulting crystalline precipitate was further added diethyl ether, then the crystals were collected by filtration, followed by washing them with ethanol and diethyl ether to give the object compound as white crystals. The yield was 6.96 g (97%). m.p. 206-210°C
¹H-NMR (DMSO-d₆, 200 MHz) δ: 2.96-3.88 (12H, m), 7.17-7.42 (5H, m), 9.65-10.11 (2H, m).
IR (KBr): 3542, 3141, 2931, 2764, 2359, 1434, 1084

cm⁻¹.

3) Synthesis of 1-[N-(tert-butoxycarbonyl)aminoacetyl]-4-(2-phenethyl)piperazine

To a suspension of 2.00 g (11.4 mmol.) of N-tert-butoxycarbonyl glycine and 2.62 g (17.1 mmol.) of 1-hydroxybenzotriazole monohydrate in acetonitrile (20 ml) was added, at room temperature, 3.28 g (17.1 mmol.) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride. The mixture was stirred for one hour.

5 To the reaction system was added a solution of 3.00 g (11.4 mmol.) of 1-(2-phenethyl)piperazine dihydrochloride, 3.47 g (22.8 mmol.) of 1,8-diazabicyclo[5.5.0]undec-7-ene (DBU) and 1.6 ml (11.5 mmol.) of triethylamine in acetonitrile (20 ml). The mixture was stirred for further one hour. The solvent was distilled off under reduced pressure. To the residue was added water, which was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of

10 hydrogencarbonate and a saturated aqueous saline solution, followed by drying over magnesium sulfate. The solvent was distilled off under reduced pressure to leave a crude product, which was purified by means of a column chromatography (methanol/ethyl acetate 5%). The solvent was distilled off under reduced pressure. The residue was recrystallized from ethyl acetate - petroleum ether to give the object compound as white crystals. The yield was 3.01 g (76%). m.p. 109-110°C

15 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.45 (9H, s), 2.45-2.56 (4H, m), 2.56-2.70 (2H, m), 2.74-2.87 (2H, m), 3.35-3.47 (2H, m), 3.60-3.73 (2H, m), 3.96 (2H, d, J=4.2 Hz), 5.45-5.60 (1H, m), 7.14-7.36 (5H, m).

20 IR (KBr): 3263, 2968, 2929, 1718, 1656, 1543, 1452, 1240, 1163, 1038, 739 cm⁻¹.

25 4) Synthesis of 1-aminoacetyl-4-(2-phenethyl)piperazine dihydrochloride

To 2.98 g (8.58 mmol.) of 1-[N-(tert-butoxycarbonyl)aminoacetyl]-4-(2-phenethyl)piperazine was added, at room temperature, 4 ml (48 mmol.) of 12N hydrochloric acid. The mixture was stirred for 30 minutes. To the reaction system was added ethanol to allow crystals to precipitate. Diethyl ether was further added, then crystals were collected by filtration and washed with ethanol and diethyl ether to give the object compound as white crystals. The yield was 2.67 g (97%).

m.p. 237-247°C (decomp.)

¹H-NMR (DMSO-d₆, 200 MHz) δ: 2.88-3.47 (8H, m), 3.51-3.76 (2H, m), 3.83-4.11 (3H, m), 4.36-4.53 (1H, m), 7.21-7.42 (5H, m), 8.16-8.38 (3H, m).

IR (KBr): 3412, 2995, 2931, 2549, 1666, 1500, 1452 cm⁻¹.

Reference Example 48

Synthesis of 1-(aminoacetyl)-4-(3-phenylpropan-1-yl)-2,3,5,6-tetrahydro-7H-1,4-diazepine dihydrochloride

1) Synthesis of tert-butyl 4-(3-phenylpropan-1-yl)-2,3,5,6-tetrahydro-7H-1,4-diazepine-1-carboxylate

To a solution of 4.50 g (22.47 mmol.) of 1-tert-butoxycarbonyl-2,3,5,6-tetrahydro-7H-1,4-diazepine in ethanol (50 ml) were added, at room temperature, 4.7 ml (33.72 mmol.) of triethylamine and 4.47 g (22.45 mmol.) of 1-bromo-3-phenylpropane. The mixture was heated under reflux for 8 hours under nitrogen atmosphere. To the reaction system were further added 4.7 ml (33.72 mmol.) of triethylamine and 4.47 g (22.45 mmol.) of 1-bromo-3-phenylpropane. The mixture was heated for 16 hours under reflux, which was cooled to room temperature. To the reaction system was added ethyl acetate, which was washed with water and a saturated aqueous saline solution, followed by drying over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by means of

a column chromatography. The solvent was distilled off under reduced pressure to give the object compound as a yellow liquid product. The yield was 5.41 g (76%).

5 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.46 (9H, s), 1.68-1.89 (4H, m), 2.46-2.53 (2H, m), 2.54-2.70 (6H, m), 3.36-3.55 (4H, m), 7.12-7.34 (5H, m).

IR (neat): 2937, 1693, 1464, 1412, 1365, 1173, 746, 700 cm⁻¹.

10 2) Synthesis of 1-(3-phenylpropan-1-yl)-2,3,5,6-tetrahydro-7H-1,4-diazepine dihydrochloride

To 5.41 g (5.41 g (16.99 mmol.) of tert-butyl 4-(3-phenylpropan-1-yl)-2,3,5,6-tetrahydro-7H-1,4-diazepine-1-carboxylate was added, at room temperature, 5 ml (60 mmol.) of 12N hydrochloric acid. The mixture 15 was stirred for 2 hours. To the reaction system was added ethanol, then the solvent was distilled off under reduced pressure to give the object compound as a pale yellow amorphous product. The yield was 5.65 g (100%).

16 ¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.91-2.33 (4H, m), 2.63 (2H, t, J=7.8 Hz), 3.02-3.84 (10H, m), 7.10-7.39 (5H, m), 9.38-10.08 (2H, m), 11.42-11.74 (1H, m).

17 3) Synthesis of 1-[N-(tert-butoxycarbonyl)aminoacetyl]-4-(3-phenylpropan-1-yl)-2,3,5,6-tetrahydro-7H-1,4-diazepine

18 To a suspension of 2.8 g (15.98 mmol.) of N-tert-butoxycarbonyl glycine and 3.67 g (23.96 mmol.) of 1-hydroxybenzotriazole monohydrate was added, at room temperature, 4.6 g (24.0 mmol.) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride. The 23 mixture was stirred for one hour. To the reaction system, was added an acetonitrile solution (20 ml) of 5.65 (16.99 mmol.) of 1-(3-phenylpropan-1-yl)-2,3,5,6-tetrahydro-7H-1,4-diazepine dihydrochloride, 5.17 g (33.96 mmol.) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 2.3 ml (16.5 mmol.) of triethylamine. The 28 mixture was stirred for 2 hours. The solvent was

distilled off under reduced pressure. To the residue was added water, which was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous saline solution, which was dried over magnesium sulfate, followed by distilling off the solvent under reduced pressure. The crude product thus-obtained was purified by means of a column chromatography (methanol/ethyl acetate 10-20%). The solvent was distilled off under reduced pressure to afford the object compound as a pale yellow oily product. The yield was 5.64 g (94%).
¹H-NMR (CDCl₃, 200 MHz) δ: 1.45 (9H, s), 1.68-1.97 (4H, m), 2.42-2.55 (2H, m), 2.55-2.74 (6H, m), 3.36-3.49 (2H, m), 3.58-3.72 (2H, m), 3.90-3.99 (2H, m), 5.50-5.62 (1H, m), 7.12-7.35 (5H, m).
IR (neat): 3415, 2935, 1711, 1651, 1456, 1168 cm⁻¹.
4) Synthesis of 1-(aminoacetyl)-4-(3-phenylpropan-1-yl)-2,3,5,6-tetrahydro-7H-1,4-diazepine dihydrochloride
To 5.64 g (15.02 mmol.) of 1-[N-(tert-butoxycarbonyl)aminoacetyl]-4-(3-phenylpropan-1-yl)-2,3,5,6-tetrahydro-7H-1,4-diazepine was added, at room temperature, 5 ml (60 mmol.) of 12N hydrochloric acid. The mixture was stirred for 20 minutes. To the reaction system was added ethanol. The solvent was distilled off under reduced pressure to leave the object compound as a pale yellow amorphous product. This compound was used for the subsequent reaction without purification. The yield was 4.69 g (90%).
¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.94-2.18 (4H, m), 2.56-2.71 (2H, m), 2.90-4.15 (12H, m), 7.15-7.37 (5H, m), 8.14-8.42 (3H, m).
IR (KBr): 3353, 2949, 1661, 1470 cm⁻¹.
Reference Example 49
Synthesis of 1-(aminoacetyl)-4-(2-phenethyl)-2,3,5,6-tetrahydro-7H-1,4-diazepine dihydrochloride

1) Synthesis of tert-butyl 4-(2-phenethyl)-2,3,5,6-tetrahydro-7H-1,4-diazepine-1-carboxylate

To a solution of 4.61 g (20.0 mmol.) of 1-tert-butoxycarbonyl-2,3,5,6-tetrahydro-7H-1,4-diazepine in ethanol (50 ml) were added, at room temperature, 6.5 ml (46.6 mmol.) of triethylamine and 6.3 g (34.0 mmol.) of phenethyl bromide. The mixture was heated under reflux for 16 hours under nitrogen atmosphere. To the reaction system were further added 3.0 ml (21.5 mmol.) of triethylamine and 1.0 ml (7.32 mmol.) of phenethyl bromide. The mixture was heated under reflux for 3 hours under nitrogen atmosphere. The reaction mixture was cooled to room temperature, to which was added ethyl acetate. The mixture was washed with water and a saturated aqueous saline solution, followed by drying over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by means of a column chromatography (ethyl acetate/hexane 50%-ethyl acetate). The solvent was distilled off under reduced pressure to afford the object compound as a pale yellow oily product. The yield was 5.63 g (80%).

¹H-NMR (CDCl₃, 200 MHz) δ: 1.46 (9H, s), 1.75-1.94 (2H, m), 2.63-2.87 (8H, m), 3.37-3.58 (4H, m), 7.13-7.36 (5H, m).

IR (neat): 1691 cm⁻¹.

2) Synthesis of 1-(2-phenethyl-2,3,5,6-tetrahydro-7H-1,4-diazepine dihydrochloride

To 5.63 g (18.5 mmol.) of tert-butyl 4-(2-phenethyl)-2,3,5,6-tetrahydro-7H-1,4-diazepine-1-carboxylate was added, at room temperature, 5 ml (60 mmol.) of 12N hydrochloric acid. The mixture was stirred for one hour. To the reaction system was added ethanol, which was concentrated under reduced pressure. To the resulting white crystals were added ethanol and diethyl ether. The crystals were collected by

filtration and washed with ethanol and diethyl ether to give the object compound as a white crystalline product. The yield was 4.7 g (92%)

5 ¹H-NMR (DMSO-d₆, 200 MHz) δ: 2.07-2.28 (2H, m), 2.90-3.90 (12H, m), 7.18-7.20 (5H, m), 9.36-10.09 (2H, m), 11.55-11.89 (1H, m).

IR (KBr): 2973, 2593, 1580, 1441, 1111, 1030, 1020, 747, 696 cm⁻¹.

10 3) Synthesis of 1-[N-(tert-butoxycarbonyl)aminoacetyl]-4-(2-phenethyl)-2,3,5,6-tetrahydro-7H-1,4-diazepine

15 To a suspension of 2.71 g (15.47 mmol.) of N-tert-butoxycarbonyl glycine and 3.55 g (23.2 mmol.) of 1-hydroxybenzotriazole monohydrate in acetonitrile (30 ml) was added, at room temperature, 4.45 g (23.2 mmol.) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride. The mixture was stirred for one hour. To the reaction system was added a solution of 4.5 g (16.23 mmol.) of 1-(2-phenethyl)-2,3,5,6-tetrahydro-7H-1,4-diazepine dihydrochloride, 4.94 g (32.45 mmol.) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 2.2 ml (15.78 mmol.) of triethylamine in acetonitrile. The mixture was stirred for further one hour. The solvent was distilled off under reduced pressure. To the residue was added water, which was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous saline solution, which was dried over magnesium sulfate, followed by distilling off the solvent under reduced pressure. The crude product was purified by means of a column chromatography (methanol/ethyl acetate 10 - 40%). The solvent was distilled off under reduced pressure to give the object compound as a pale yellow oily product. The yield was 5.18 g (93%).

20 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.45 (9H, s), 1.79-2.00 (2H, m), 2.61-2.82 (8H, m), 3.36-3.50 (2H, m), 3.59-

25

30

35

3.74 (2H, m), 3.89-3.99 (2H, m), 5.50-5.63 (1H, m), 7.13-7.35 (5H, m).

IR (neat): 3415, 2974, 2935, 1712, 1651, 1493, 1458, 1365, 1250, 1171, 1053, 750, 702 cm⁻¹.

5 4) Synthesis of 1-(aminoacetyl)-4-(2-phenethyl)-2,3,5,6-tetrahydro-7H-1,4-diazepine dihydrochloride

To 5.18 g (14.3 mmol.) of 1-[N-(tert-butoxycarbonyl)aminoacetyl]-4-(2-phenethyl)-2,3,5,6-tetrahydro-7H-1,4-diazepine was added, at room temperature, 5 ml (60 mmol.) of 12N hydrochloric acid. The mixture was stirred for one hour. To the reaction system was added ethanol, then the solvent was distilled off under reduced pressure. To the residue were added ethanol and diethyl ether. The resulting crystals were collected by filtration, followed by washing with diethyl ether, to give the object compound as white crystals. The yield was 4.64 g (97%).

m.p. 257-260°C (decomp.)

20 ¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.97-2.22 (2H, m), 2.93-4.14 (14H, m), 7.20-7.41 (5H, m), 8.15-8.42 (3H, m).

IR (KBr): 3374, 2948, 1661, 1470 cm⁻¹.

Reference Example 50

25 Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-aminoacetamide dihydrochloride

1) Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-(N-tert-butoxycarbonylamino)acetamide

To a suspension of 4.21 g (24.03 mmol.) of N-tert-butoxycarbonyl glycine and 5.51 g (35.98 mmol.) of 1-hydroxybenzotriazole monohydrate in acetonitrile (30 ml) was added, at room temperature, 6.90 g (36.0 mmol.) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarboxiimide hydrochloride. The mixture was stirred for one hour. To the reaction system was then added a solution of 7.00 g (24.03 mmol.) of 4-amino-1-(3-phenylpropan-1-yl)piperidine dihydrochloride, 7.32 g (48.08 mmol.) of

1,8-bicyclo[5.4.0]undec-7-ene (DBU) and 3.4 ml (24.4 mmol.) of triethylamine in acetonitrile (20 ml). The mixture was stirred for 2 hours at room temperature. The solvent was distilled off under reduced pressure.

5 To the residue was added chloroform. The mixture was washed with water and a saturated aqueous saline solution, followed by drying over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by means of a column

10 chromatography (methanol/ethyl acetate 30%). The solvent was distilled off under reduced pressure to give the object compound as a yellowish orange liquid product. The yield was 5.35 g (59%).

¹H-NMR (CDCl₃, 200 MHz) δ: 1.45 (9H, s), 1.61-1.97 (6H, m), 2.03-2.20 (2H, m), 2.32-2.43 (2H, m), 2.63 (2H, t, J=7.6 Hz), 2.74-2.93 (2H, m), 3.66-3.87 (1H, m), 3.75 (2H, d, J=6.0 Hz), 4.99-5.15 (1H, m), 5.92-6.06 (1H, m), 7.12-7.33 (5H, m).

15 IR (neat): 3413, 3305, 2937, 1713, 1670, 1539, 1369, 1250, 1169 cm⁻¹.

20 2) Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-aminoacetamide dihydrochloride

To 5.35 g (14.25 mmol.) of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-(N-tert-butoxy-carbonylamino)acetamide was added, at room temperature, 10 ml (120 mmol.) of 12N hydrochloric acid. The mixture was stirred for one hour. To the reaction system was added ethanol, which was then concentrated under reduced pressure. To the concentrate were added 2-propanol and diethyl ether. The resulting crystals were collected by filtration, followed by washing with 2-propanol and diethyl ether, to give the object compound as a pale yellow crystalline product. The yield was 4.20 g (85%).

25 30 35 m.p. 258-261°C

¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.67-2.21 (6H, m), 2.56-

2.62 (2H, m), 2.64-3.12 (4H, m), 3.24-4.13 (5H, m), 7.11-7.37 (5H, m), 8.04-8.30 (3H, m), 8.65-8.76 (1H, m).

IR (KBr): 3175, 3054, 2996, 1690, 1568, 1505, 1437, 5 1269, 912, 764, 706 cm⁻¹.

Reference Example 51

Synthesis of 4-(4-aminobutan-1-yl)-1-benzoylpiperazine dihydrochloride

1) Synthesis of 1-benzoyl-4-benzylpiperazine

10 To a solution of 25.72 g (145.92 mmol.) of 1-benzylpiperazine and 31 ml (222.4 mmol.) of triethylamine in acetonitrile (250 ml) was added at 0 °C 21.44 g (152.5 mmol.) of benzoyl chloride. The mixture was stirred for 16 hours at room temperature.

15 The solvent was distilled off under reduced pressure. To the residue were added water and a saturated aqueous solution of sodium hydrogencarbonate, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous saline solution, which was dried over magnesium sulfate, followed by concentration. The concentrate was purified by means of a column chromatography (ethyl acetate/hexane 50% - ethyl acetate). The solvent was distilled off under reduced pressure. The resulting crystals were

20 collected by filtration and washed with hexane to give the object compound as a pale brown crystalline product. The yield was 38.41 g (94%)

¹H-NMR (CDCl₃, 200 MHz) δ: 2.82-2.62 (4H, m), 3.31-3.58 (2H, m), 3.54 (2H, s), 3.65-3.89 (2H, m), 7.18-30 7.36 (5H, m), 7.40 (5H, s).

IR (KBr): 1628, 1437, 1279, 997, 739, 704 cm⁻¹.

2) Synthesis of 1-benzoylpiperazine formate

To a suspension of 20.02 g (71.4 mmol.) of 1-benzoyl-4-benzylpiperazine and 1.0 g of 10% palladium carbon in methanol (200 ml) was added dropwise gradually, at room temperature, 9.9 g (215 mmol.) of

formic acid. The mixture was stirred for 6 hours. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. To the concentrate was added ethyl acetate, and the mixture was concentrated. To the resulting crystals were added ethyl acetate and hexane. The mixture was subjected to filtration to collect the crystals, followed by washing with ethyl acetate and hexane to give the object compound as a white crystalline product. The yield was 10 15.97 g (95%).

m.p. 88-90°C

$^1\text{H-NMR}$ (DMSO-d₆, 200 MHz) δ: 2.74-2.95 (4H, m), 3.24-3.73 (4H, m), 7.34-7.49 (5H, m), 8.29 (1H, s).

IR (KBr): 3433, 2937, 1660, 1626, 1446, 1249, 1404, 15 1282, 1242, 1007, 781, 739, 708 cm⁻¹.

3) Synthesis of 4-(4-aminobutan-1-yl)-1-benzoypiperazine dihydrochloride

A solution of 5.0 g (21.16 mmol.) of 1-benzoypiperazine formate, 5.97 g (21.16 mmol.) of 4-bromobutylphthalimide and 9.0 ml (64.57 mmol.) of triethylamine in ethanol (50 ml) was heated for 40 hours under reflux. The reaction mixture was cooled to room temperature, to which was added water. The mixture was subjected to extraction with ethyl acetate. 20 The organic layer was washed with a saturated aqueous saline solution, which was then dried over magnesium sulfate, followed by distilling off the solvent under reduced pressure to leave a crude product. The crude product was purified by means of a column chromatography (methanol/ethyl acetate 5 - 10%). The solvent was distilled off under reduced pressure to give N-[4-(4-benzoypiperazin-1-yl)butan-1-yl]phthalimide (6.99 g) as yellow oil. To a solution of 6.99 g of this compound in ethanol (50 ml) was 25 added, at room temperature, 1.34 g (26.8 mmol.) of hydrazine monohydrate. The mixture was heated for 2 30 35

hours under reflux. The reaction mixture was cooled to room temperature. The resulting white solid substance was filtered off, and the filtrate was concentrated under reduced pressure. To the concentrate was added 5 water, which was subjected to extraction with chloroform. The organic layer was washed with a saturated aqueous saline solution, which was dried over magnesium sulfate, followed by distilling off the solvent under reduced pressure to leave crude 4-(4- 10 aminobutan-1-yl)-1-benzoylpiperazine. To an ethanol solution of this compound was added, at room temperature, 5 ml (60 mmol.) of 12N hydrochloric acid. The mixture was stirred for one hour at room temperature. The reaction mixture was concentrated 15 under reduced pressure, to which was added diethyl ether. The resulting crystals were collected by filtration and washed with ethanol and diethyl ether to give the object compound as a white crystalline product. The yield was 2.92 g (41%).

20 m.p. 257-260°C (decomp.)

¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.51-1.88 (4H, m), 2.71- 2.92 (2H, m), 2.94-3.20 (4H, m), 3.27-3.65 (6H, m), 7.41-7.55 (5H, m), 7.88-8.13 (3H, m).

IR (KBr): 2931, 1632, 1460, 1429, 1284, 714 cm⁻¹.

25 Reference Example 52

Synthesis of 4-(3-aminopropan-1-yl)-1-benzoylpiperazine dihydrochloride

A solution of 5.0 g (21.16 mmol.) of 1- 30 benzoylpiperazine formate, 5.67 g (21.15 mmol.) of 3- bromopropylphthalimide and 9.0 ml (64.57 mmol.) of triethylamine in ethanol (50 ml) was heated under reflux for 18 hours under nitrogen atmosphere. The reaction mixture was cooled to room temperature, to which was added water. The mixture was subjected to 35 extraction with ethyl acetate. The organic layer was washed with a saturated aqueous saline solution, which

was dried over magnesium sulfate, followed by distilling off the solvent under reduced pressure. The resulting crude product was purified by means of a column chromatography (methanol/ethyl acetate 5%), 5 followed by distilling off the solvent under reduced pressure, to give N-[3-(4-benzoylpiperazin-1-yl)propan-1-yl]phthalimide (6.22 g) as yellow oil. To an ethanol (50 ml) solution of this compound (6.22 g) was added, at room temperature, 1.24 g (24.8 mmol.) of hydrazine 10 monohydrate. The mixture was heated for 2 hours under reflux. The reaction mixture was cooled to room temperature, then the resulting white solid substance was filtered off. The filtrate was concentrated under reduced pressure. To the concentrate was added water, 15 which was subjected to extraction with chloroform. The organic layer was washed with a saturated aqueous saline solution, followed by drying over magnesium sulfate. the solvent was distilled off under reduced pressure to leave crude 4-(3-aminopropan-1-yl)-1- 20 benzoylpiperazine. To an ethanol solution of this crude 4-(3-aminopropan-1-yl)-1-benzoylpiperazine was added, at room temperature, 3 ml (36 mmol.) of 12N hydrochloric acid. The mixture was stirred for one hour at room temperature. The reaction mixture was 25 concentrated under reduced pressure. To the concentrate was added diethyl ether. The resulting crystals were collected by filtration and washed with ethanol and diethyl ether to give the object compound as a white crystalline product. The yield was 1.80 g 30 (27%).

¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.94-2.11 (2H, m), 2.83- 3.64 (12H, m), 7.42-7.54 (5H, m).

IR (KBr): 3433, 2997, 2929, 1630, 1458, 1429, 1284 cm⁻¹.

35 Reference Example 53

Synthesis of cis-4-(1-benzyl-2,6-dimethyl-piperazin-1-

yl) butan-1-ylamine

1) Synthesis of cis-1-tert-butoxycarbonyl-3,5-dimethyl piperazine

To an ethanol (42 ml) solution of 5.0 g (21.07 mmol.) of cis-3,5-dimethyl piperazine was added, at room temperature, 2.5 ml (32.3 mmol.) of di-tert-butyl dicarbonate. The mixture was stirred for one hour. The solvent was distilled off under reduced pressure. To the residue was added water, which was subjected to extraction with chloroform. The organic layer was washed with a saturated aqueous saline solution, which was dried over magnesium sulfate. The solvent was distilled off under reduced pressure to give the object compound as a pale yellow solid product. The yield was 15 5.77 g (72%).

¹H-NMR (CDCl₃, 200 MHz) δ: 1.06 (6H, d, J=6.4 Hz), 1.46 (9H, s), 2.21-2.40 (2H, m), 2.68-2.86 (2H, m), 3.79-4.09 (2H, m).

IR (KBr): 3319, 2972, 1680, 1425, 1367, 1315, 1267, 20 1173, 1144, 1072, 895, 866, 797 cm⁻¹.

2) Synthesis of cis-1-tert-butoxycarbonyl-3,5-dimethyl-4-benzyl piperazine

To a suspension of 10 g (46.66 mmol.) of cis-1-tert-butoxycarbonyl-3,5-dimethyl piperazine and 12.90 g (93.3 mmol.) of potassium carbonate in N,N-dimethylformamide (100 ml) was added, at room temperature, 11.97 g (70 mmol.) of benzyl bromide. The mixture was stirred for 16 hours at 120°C. To the reaction system was added water, which was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous saline solution, which was dried over magnesium sulfate, followed by distilling off the solvent. The residue was purified by means of a column chromatography (ethyl acetate/hexane 30%) to give the object compound as a pale yellow oily product. The yield was 13.56 g (95%).

¹H-NMR (CDCl₃, 200 MHz) δ: 1.04 (6H, d, J=5.8 Hz), 1.45 (9H, s), 2.45-2.75 (4H, m), 3.67-3.92 (2H, m), 3.81 (2H, s), 7.15-7.39 (5H, m).

IR (neat): 2980, 1693, 1423, 1136, 1061, 924, 883, 766, 729, 700 cm⁻¹.

3) Synthesis of cis-1-benzyl-2,6-dimethyl piperazine

To 13.56 g (44.54 mmol.) of cis-1-tert-butoxycarbonyl-3,5-dimethyl-4-benzyl piperazine was added, at room temperature, 15 ml (180 mmol.) of 12N

hydrochloric acid. The mixture was stirred for one hour. To the reaction system was added at 0 °C, a 8N aqueous solution of sodium hydroxide to make pH of the reaction system alkaline, which was then subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous saline solution, which was dried over magnesium sulfate. The solvent was distilled off under reduced pressure to leave the object compound as a yellow oily product. This compound was used for the subsequent reaction without purification. The yield was 7.67 g (95%).

¹H-NMR (CDCl₃, 200 MHz) δ: 1.02 (6H, d, J=5.8 Hz), 2.39-2.63 (4H, m), 2.88 (2H, d, J=9.8 Hz), 3.83 (2H, s), 7.15-7.41 (5H, m).

IR (KBr): 3271, 2970, 2816, 1460, 1379, 1315, 1200, 1158, 1140, 1603, 729 cm⁻¹.

4) Synthesis of N-cis-[4-(1-benzyl-2,6-dimethyl piperazin-1-yl)butan-1-yl]phthalimide

To a solution of 3.5 g (17.13 mmol.) of cis-1-benzyl-2,6-dimethyl piperazine and 5.0 ml (35.87 mmol.) of triethylamine in ethanol (30 ml) was added, at room temperature, 4.83 g (17.12 mmol.) of 4-bromobutyl phthalimide. The mixture was heated under reflux for 18 hours under nitrogen atmosphere. The reaction mixture was cooled to room temperature, to which was added water, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous

saline solution, which was dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by means of a column chromatography (ethyl acetate/hexane 75% - ethyl acetate) to give the object compound as an orange oily product. The yield was 5.86 g (84%).

5 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.02 (6H, d, J=6.4 Hz),
10 1.44-1.87 (6H, m), 2.23-2.35 (2H, m), 2.55-2.78
 (4H, m), 3.70 (2H, t, J=7.2 Hz), 3.81 (2H, s),
15 7.16-7.37 (5H, m), 7.66-7.75 (2H, m), 7.78-7.86
 (2H, m).

IR (neat): 2939, 2812, 1772, 1714, 1396, 1369, 1155,
1076, 1047, 721 cm⁻¹.

15 5) Synthesis of cis-4-(1-benzyl-2,6-dimethylpiperazin-1-yl)butan-1-ylamine

20 To an ethanol (20 ml) solution of 5.86 g (14.45 mmol.) of N-cis-[4-(1-benzyl-2,6-dimethylpiperazin-1-yl) butan-1-yl]phthalimide was added, at room temperature, 1.08 g (21.57 mmol.) of hydrazine monohydrate. The mixture was heated for two hours under reflux. The reaction mixture was cooled to room temperature, then the resulting white solid matter was filtered off. From the filtrate, the solvent was distilled off under reduced pressure. To the residue were added an aqueous solution of sodium hydroxide and sodium chloride. The mixture was subjected to extraction with chloroform. The organic layer was washed with a saturated aqueous saline solution, which was dried over magnesium sulfate. The solvent was distilled off under reduced pressure to give the object compound as an orange oily product. This compound was used for the subsequent reaction without purification.

25 The yield was 3.64 g (91%).

30 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.04 (6H, d, J=6.2 Hz),
35 1.36-1.63 (4H, m), 1.78-1.89 (2H, m), 2.22-2.33
 (2H, m), 2.57-2.82 (6H, m), 3.83 (2H, s), 7.14-

7.40 (5H, m).

IR (neat): 3359, 2936, 2812, 1468, 1323, 1153, 1076, 729, 698 cm⁻¹.

Reference Example 54

5 **Synthesis of cis-4-(3-aminopropyl)-1-benzyl-2,6-dimethyl piperazine**

1) **Synthesis of N-cis-[3-(4-benzyl-3,5-dimethyl piperazine-1-yl)propan-1-yl]phthalimide**

To an ethanol (40 ml) solution of 4.06 g (19.87 mmol.) of *cis*-1-benzyl-2,6-dimethyl piperazine and 5.6 ml (40.18 mmol.) of triethylamine was added, at room temperature, 5.33 g (19.88 mmol.) of 3-bromomopropyl phthalimide. The mixture was heated under reflux for 20 hours under nitrogen atmosphere. The reaction mixture was cooled to room temperature. To the reaction system was added water, which was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous saline solution and dried over magnesium sulfate, followed by distilling off the solvent under reduced pressure. The residue was purified by means of a column chromatography (ethyl acetate/hexane 50 ~ 75%) to give the object compound as a yellow oily product. The yield was 6.59 g (85%).

¹H-NMR (CDCl₃, 200 MHz) δ: 0.99 (6H, d, J=5.8 Hz), 1.71-1.93 (4H, m), 2.31-2.38 (2H, m), 2.41-2.55 (2H, m), 2.65-2.76 (2H, m), 3.71-3.78 (2H, m), 3.73 (2H, s), 7.13-7.37 (5H, m), 7.65-7.74 (2H, m), 7.78-7.86 (2H, m).

IR (neat): 2964, 2937, 2812, 1772, 1714, 1466, 1396, 1369, 1329, 1200, 1155, 1090, 1038, 721 cm⁻¹.

2) **Synthesis of cis-4-(3-aminopropyl-1-benzyl-2,6-dimethyl piperazine**

To an ethanol (30 ml) solution of 6.59 g (16.8 mmol.) of *N*-*cis*-[3-(4-benzyl-3,5-dimethylpiperazin-1-yl) propan-1-yl]phthalimide was added, at room temperature, 1.26 g (25.2 mmol.) of hydrazine

monohydrate. The mixture was heated for one hour under reflux. The reaction mixture was cooled to room temperature. The resulting white solid matter was filtered off. From the filtrate, the solvent was distilled off under reduced pressure. To the residue was added an aqueous solution of sodium hydroxide, which was subjected to extraction with chloroform. The organic layer was washed with a saturated aqueous saline solution and dried over magnesium sulfate. The solvent was distilled off under reduced pressure to leave the object compound as a yellow oily product. This compound was used for the subsequent reaction without purification. The yield was 3.85 g (88%).

¹H-NMR (CDCl₃, 200 MHz) δ: 1.04 (6H, d, J=6.2 Hz), 1.57-1.70 (2H, m), 1.83 (2H, t, J=10.8 Hz), 2.29-2.37 (2H, m), 2.61-2.83 (6H, m), 3.83 (2H, s), 7.18-7.32 (5H, m).

IR (neat): 3361, 3284, 2937, 2812, 1603, 1493, 1375, 1323, 1153, 1076, 727, 698 cm⁻¹.

Reference Example 55
Synthesis of cis-1-(2-aminoethyl)-4-(3-phenylpropan-1-yl)-3,5-dimethyl piperazine
1) Synthesis of cis-1-tert-butoxycarbonyl-3,5-dimethyl-4-(3-phenylpropan-1-yl)piperazine

To a suspension of 10 g (46.66 mmol.) of cis-1-tert-butoxycarbonyl-3,5-dimethyl piperazine and 12.90 g (93.3 mmol.) of potassium carbonate in N,N-dimethylformamide (50 ml) was added, at room temperature, 11.15 g (56 mmol.) of 1-bromo-3-phenylpropane. The mixture was stirred for 40 hours at 120°C, which was then cooled to room temperature. To the reaction system was added water, which was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous saline solution and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The

residue was purified by means of a column chromatography (ethyl acetate/hexane 20 ~ 30%) to give the object compound as a yellow oily product. The yield was 12.21 g (79%).

5 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.00 (6H, d, J=5.8 Hz), 1.45
 (9H, s), 1.57-1.69 (2H, m), 2.43-2.62 (6H, m),
 2.67-2.85 (2H, s), 3.68-3.96 (2H, m), 7.13-7.35
 (5H, m).
IR (neat): 2974, 2931, 2856, 1695, 1454, 1427, 1273,
10 1248, 1174, 1142, 748, 700 cm⁻¹.

10 2) Synthesis of cis-1-(3-phenylpropan-1-yl)-2,6-dimethyl-piperazine

To 11.76 g (35.4 mmol.) of cis-1-tert-butoxycarbonyl-3,5-dimethyl-4-(3-phenylpropan-1-yl)piperazine was added, at room temperature, 10 ml (120 mmol.) of 12N hydrochloric acid. The mixture was stirred for one hour. To the reaction system was added water. Impurities were removed by extraction with ethyl acetate. The solution was made alkaline by the addition of an aqueous solution of sodium hydroxide, which was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous saline solution, which was dried over magnesium sulfate. The solvent was distilled off under reduced pressure to give the object compound as a yellow oily product. This compound was used for the subsequent reaction without purification. The yield was 5.51 g (67%).

15 ¹H-NMR (CDCl₃, 200 MHz) δ: 0.98 (6H, d, J=5.8 Hz),
 1.66-1.84 (2H, m), 2.43-2.59 (6H, m), 2.74-2.88
 (4H, s), 7.13-7.35 (5H, m).
IR (neat): 3267, 2962, 2937, 2818, 1689, 1454, 1373,
20 1319, 1205, 1157, 1074, 924, 748, 700 cm⁻¹.

25 3) Synthesis of N-cis-[2-[4-(3-phenylpropan-1-yl)-3,5-dimethyl piperazin-1-yl]ethan-1-yl]phthalimide

To a solution of 5.67 g (21.5 mmol.) of phthalimide acetaldehyde diethyl acetal in acetic acid (18 ml) was added, at room temperature, 2.1 ml (25.2 mmol.) of 12N hydrochloric acid. The mixture was stirred for 2 hours at 60 °C. The reaction mixture was cooled to room temperature, which was neutralized with 2.54 g (30.2 mmol.) of sodium hydrogencarbonate. To the reaction system was added a solution of 5.00 g (21.5 mmol.) of cis-1-(3-phenylpropan-1-yl)-2,6-dimethyl piperazine in methanol (40 ml). The mixture was stirred for one hour. To the reaction system was added 6.84 g (32.27 mmol.) of sodium triacetoxylborohydride divided into three portions with the interval of 30 minutes. The mixture was stirred for 18 hours. The solvent was distilled off under reduced pressure. The residue was neutralized with acetic acid, which was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous saline solution and dried over magnesium sulfate, followed by concentration to leave a crude product. The crude product was purified by means of a column chromatography (methanol/ethyl acetate 5%) to give the object compound as a pale brown oily product. The yield was 7.37 g (85%).

¹H-NMR (CDCl₃, 200 MHz) δ: 0.99 (6H, d, J=6.2 Hz), 1.54-1.74 (2H, m), 1.81-1.93 (2H, m), 2.44-2.63 (6H, m), 2.68-2.86 (2H, m), 3.79 (2H, t, J=6.8 Hz), 7.11-7.32 (5H, m), 7.64-7.74 (2H, m), 7.80-7.87 (2H, m).

IR (neat): 2945, 2814, 1774, 1713, 1394, 1327, 1242, 1159, 1076, 1026, 721 cm⁻¹.

4) Synthesis of cis-1-(2-aminoethyl)-4-(3-phenylpropan-1-yl)-3,5-dimethyl piperazine
To an ethanol (50 ml) solution of 7.28 g (17.95 mmol.) of N-cis-[2-[4-(3-phenylpropan-1-yl)-3,5-dimethyl piperazin-1-yl]ethan-1-yl]phthalimide was

added, at room temperature, 1.3 ml (26.8 mmol.) of hydrazine monohydrate. The mixture was heated under reflux for 2 hours, which was cooled to room temperature. The resulting white solid matter was 5 filtered off. From the filtrate, the solvent was distilled off under reduced pressure. To the residue was added an aqueous solution of sodium hydroxide, which was subjected to extraction with chloroform. The organic layer was washed with a saturated aqueous 10 saline solution and dried over magnesium sulfate. The solvent was then distilled off under reduced pressure to give the object compound as a yellow oily product. This compound was used for the subsequent reaction without purification. The yield was 4.35 g (88%). 15 $^1\text{H-NMR}$ (CDCl_3 , 200 MHz) δ : 1.00 (6H, d, $J=6.2$ Hz), 1.65-1.90 (4H, m), 2.34 (2H, t, $J=6.3$ Hz), 2.54 (2H, t, $J=7.5$ Hz), 2.61-2.85 (8H, m), 7.13-7.34 (5H, m).
IR (neat): 3359, 3262, 2960, 2810, 1691, 1603, 1456, 20 1371, 1323, 1153, 1076, 748, 700 cm^{-1} .

Reference Example 56

Synthesis of trans-1-(4-aminobutyl)-4-benzyl-2,5-dimethyl piperazine

1) Trans-1-tert-butoxycarbonyl-2,5-dimethyl piperazine

25 To an ethanol (200 ml) solution of 25.18 g (220.5 mmol.) of trans-2,5-dimethyl piperazine was added, at room temperature, 9.63 g (44.1 mmol.) of di-tert-butyl dicarbonate. The mixture was stirred for 2 hours. The solvent was distilled off under reduced pressure. To 30 the residue was added water, which was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous saline solution, which was dried over magnesium sulfate. The solvent was distilled off under reduced pressure to give the object 35 compound as a pale brown oily product. The yield was 9.36 g (99%).

¹H-NMR (CDCl₃, 200 MHz) δ: 1.17 (3H, d, J=7.0 Hz), 1.21 (3H, d, J=6.6 Hz), 1.46 (9H, s), 2.48 (1H, dd, J=12.8 & 3.0 Hz), 3.05-3.26 (3H, m), 3.55 (1H, dd, J=13.2 & 1.6 Hz), 4.03-4.19 (1H, m).

5 2) Synthesis of trans-1-butoxycarbonyl-2,5-dimethyl-4-benzyl piperazine

To an acetonitrile (40 ml) solution of 4.5 g (21.0 mmol.) of trans-1-tert-butoxycarbonyl-2,5-dimethyl piperazine and 5.9 ml (42.3 mmol.) of triethylamine was added, at room temperature, 3.2 ml (26.9 mmol.) of benzyl bromide. The mixture was heated for 24 hours under reflux. The solvent was distilled off under reduced pressure. To the residue was added water. The mixture was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous saline solution, which was dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by means of a column chromatography (ethyl acetate/hexane 10%) to give the object compound as a pale yellow oily product.

20 The yield was 5.17 g (81%).
¹H-NMR (CDCl₃, 200 MHz) δ: 0.98 (3H, d, J=6.6 Hz), 1.23 (3H, d, J=7.0 Hz), 1.46 (9H, s), 2.19 (1H, d, J=13.0 Hz), 2.70 (1H, dd, J=12.0 & 4.4 Hz), 2.85-3.04 (1H, m), 3.31 (1H, dd, J=12.8 & 3.8 Hz), 3.46 (1H, d, J=13.6 Hz), 3.62 (1H, d, J=13.6 Hz), 3.65 (1H, dd, J=13.0 & 0.8 Hz), 4.10-4.28 (1H, m), 7.18-7.42 (5H, m).

25 IR (neat): 2929, 2819, 1691, 1417, 1367, 1317, 1267, 1163, 1059, 864, 756, 708 cm⁻¹.

30 3) Synthesis of trans-1-benzyl-2,5-dimethylpiperazine dihydrochloride

To 9.76 g (32.06 mmol.) of trans-1-tert-butoxycarbonyl-2,5-dimethyl-4-benzyl piperazine was added, at room temperature, 10 ml (120 mmol.) of 12N hydrochloric acid. The mixture was stirred for one

hour. The solvent was distilled off under reduced pressure. To the residue was added 2-propanol, which was further concentrated. To the concentrate was added diethyl ether. The resulting crystals were collected by filtration and washed with 2-propanol and diethyl ether to give the object compound as white crystals. The yield was 7.97 g (90%).

5 ¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.22 (3H, d, J=6.6 Hz),
10 1.59 (3H, d, J=5.4 Hz), 2.84-3.83 (6H, m), 3.96-
 4.29 (1H, m), 4.57-4.74 (1H, m), 7.36-7.52 (3H,
 m), 7.56-7.72 (2H, m), 9.93-10.25 (2H, m).
IR (neat): 2767, 2694, 2507, 2266, 1454, 1333, 1186,
1061, 991, 928, 766, 706 cm⁻¹.

15 4) Synthesis of N-trans-[4-(4-benzyl-2,5-dimethylpiperazin-1-yl)butan-1-yl]phthalimide
To a suspension of 4.00 g (14.43 mmol.) of trans-1-benzyl-2,5-dimethylpiperazine dihydrochloride, 4.88 g (17.3 mmol.) of 4-bromobutyl phthalimide and 8.0 ml (57.4 mmol.) of triethylamine in acetonitrile (50 ml) was added, at room temperature, 2.59 g (17.3 mmol.) of sodium iodide. The mixture was heated under reflux for 20 hours under nitrogen atmosphere. The solvent was distilled off under reduced pressure. To the residue was added water. The mixture was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous saline solution and dried over magnesium sulfate, followed by distilling off the solvent. The residue was purified by means of a column chromatography (ethyl acetate - methanol/ethyl acetate 5%) to give the object compound as a brown oily product. The yield was 3.97 g (68%).

20 ¹H-NMR (CDCl₃, 200 MHz) δ: 0.95 (3H, d, J=5.8 Hz), 1.15
25 (3H, d, J=6.0 Hz), 1.43-1.77 (4H, m), 1.82-1.93
 (2H, m), 2.08 (2H, t, J=10.8 Hz), 2.16-2.51 (3H,
30 m), 2.59 (1H, dd, J=11.4 & 2.8 Hz), 2.70-2.79 (1H,
 m), 2.82 (1H, dd, J=11.4 & 2.8 Hz), 3.06 (1H, d,

J=13.2 Hz), 3.70 (2H, t, J=7.0 Hz), 4.08 (1H, d, J=13.2 Hz), 7.16-7.34 (5H, m), 7.65-7.76 (2H, m), 7.78-7.89 (2H, m).

IR (neat): 2939, 2800, 1770, 1713, 1441, 1396, 1371, 1336, 1182, 1066, 1041, 719 cm⁻¹.

5 5) Synthesis of trans-1-(4-aminobutyl)-4-benzyl-2,5-dimethyl piperazine

To an ethanol (20 ml) solution of 3.97 g (9.79 mmol.) of N-trans-[4-(4-benzyl-2,5-dimethyl-piperazin-1-yl)butan-1-yl]phthalimide was added, at room 10 temperature, 0.74 g (14.8 mmol.) of hydrazine monohydrate. The mixture was heated for 2 hours under reflux. The reaction mixture was cooled to room 15 temperature. The resulting white solid matter was filtered off. From the filtrate, the solvent was distilled off. To the residue was added an aqueous solution of sodium hydroxide. The mixture was subjected to extraction with chloroform. The organic layer was washed with a saturated aqueous saline 20 solution and dried over magnesium sulfate. The solvent was distilled off under reduced pressure to leave the object compound as a yellow oily product. This compound was used for the subsequent reaction without purification. The yield was 2.31 g (86%).

25 ¹H-NMR (CDCl₃, 200 MHz) δ: 0.95 (3H, d, J=6.2 Hz), 1.16 (3H, d, J=5.8 Hz), 1.34-1.55 (4H, m), 1.81-1.91 (1H, m), 2.02-2.13 (1H, m), 2.14-2.52 (4H, m), 2.60 (1H, dd, J=11.4 & 2.6 Hz), 2.65-2.76 (2H, m), 2.83 (1H, dd, J=1.0 & 3.0 Hz), 3.07 (1H, d, J=13.6 Hz), 4.08 (1H, d, J=13.2 Hz), 7.19-7.36 (5H, m).

30 IR (neat): 3363, 3280, 2935, 2802, 1603, 1450, 1377, 1336, 1178, 1153, 1068, 833, 739, 700 cm⁻¹.

Reference Example 57

Synthesis of 1-(2-aminoethan-1-yl)-2,6-dioxo-4-(3-phenylpropan-1-yl)piperazine dihydrochloride

35 1) Synthesis of 4-benzyl-1-[2-(tert-

butoxycarbonylamino) ethan-1-yl)-2,6-dioxopiperazine

To a suspension of 9.75 g (43.68 mmol.) of benzyl

iminodiacetic acid in tetrahydrofuran (129 ml) was
added, at room temperature under nitrogen atmosphere,

5 15.58 g (96.08 mmol.) of carbonyldiimidazole. The
mixture was heated for one hour under reflux. To the

reaction system was added a solution of 7.00 g (43.69
mmol.) of 1-tert-butoxycarbonyl ethylenediamine in

tetrahydrofuran (20 ml). The mixture was heated for 21
hours under reflux. The solvent was distilled off

10 under reduced pressure. The residue was dissolved in
ethyl acetate. The solution was washed twice with 0.5
N hydrochloric acid (200 ml, 50 ml), which was further

washed with water and a saturated aqueous saline

15 solution, followed by drying over magnesium sulfate and
concentration. The concentrate was washed by means of

a column chromatography (ethyl acetate/hexane 50%) to
give the object compound as a colorless crystals. The

yield was 8.65 g (57%).

20 $^1\text{H-NMR}$ (CDCl_3 , 200 MHz) δ : 1.41 (9H, s), 3.26-3.45 (2H,
m), 3.41 (4H, s), 3.62 (2H, s), 3.91 (2H, t, $J=5.6$

Hz), 4.66-4.81 (1H, m), 7.24-7.41 (5H, m).

IR (KBr): 3404, 2976, 1768, 1687, 1680, 1516, 1352,
1228, 1164, 704 cm^{-1} .

25 2) Synthesis of 1-[2-(tert-butoxycarbonylamino)ethan-1-

yl]-2,6-dioxopiperazine

A solution of 4.0 g (11.5 mmol.) of 4-benzyl-1-[2-(tert-

butoxycarbonylamino)ethan-1-yl]-2,6-

dioxopiperazine and 0.37 g of 10% palladium carbon in

30 methanol (100 ml) was stirred for 20 hours under

hydrogen atmosphere. The palladium carbon was filtered

off, followed by distilling off the solvent under

reduced pressure to give the object compound as

colorless crystals. The yield was 3.4 g (100%).

35 $^1\text{H-NMR}$ (CDCl_3 , 200 MHz) δ : 1.41 (9H, s), 3.26-3.40 (2H,
m), 3.68 (4H, s), 3.95 (2H, t, $J=5.4$ Hz), 4.74-

4.90 (1H, m).

IR (KBr): 3369, 2981, 1730, 1687, 1664, 1537, 1367, 1340, 1267, 1254, 1180, 868 cm⁻¹.

4) Synthesis of 1-(tert-butoxycarbonylamino)-2,6-dioxo-
5 4-(3-phenylpropan-1-yl)piperazine

To a solution of 3.01 g (11.7 mmol.) of 1-[2-(tert-butoxycarbonylamino)ethan-1-yl]-2,6-dioxopiperazine and 1.57 g (11.7 mmol.) of dihydrocinnamic aldehyde in tetrahydrofuran (50 ml) was added 3.72 g (17.6 mmol.) of sodium triacetoxyborohydride. The mixture was stirred for 18 hours at room temperature. The reaction mixture was poured into water to suspend the reaction, which was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous saline solution, which was dried over magnesium sulfate, followed by concentration. The concentrate was purified by means of a column chromatography (ethyl acetate/hexane 30-50%), followed by recrystallization (ethyl acetate-hexane) to give the object compound as colorless crystals. The yield was 2.77 g (63%).

¹H-NMR (CDCl₃, 200 MHz) δ: 1.42 (9H, s), 1.73-1.88 (2H, m), 2.65 (2H, t, J=7.5 Hz), 3.20-3.42 (2H, m), 3.39 (4H, m), 3.92 (2H, t, J=5.7 Hz), 4.68-4.82 (1H, m), 7.10-7.35 (5H, m).

25 IR (KBr): 3365, 2983, 1740, 1689, 1682, 1672, 1531, 1365, 1348, 1265, 1228, 1174, 1138, 964, 748, 696, 642 cm⁻¹.

30 5) Synthesis of 1-(2-aminoethan-1-yl)-2,6-dioxo-4-(3-phenylpropan-1-yl)piperazine dihydrochloride

To a solution of 2.67 g (7.11 mmol.) of 1-(tert-butoxycarbonylamino)-2,6-dioxo-4-(3-phenylpropan-1-yl)piperazine in ethanol (30 ml) was added, at room temperature, 5 ml (60 mmol.) of 12N hydrochloric acid. The mixture was stirred for 16 hours, which was then concentrated under reduced pressure. The resulting

crystals were collected by filtration and washed with ethanol and diethyl ether to give the object compound as colorless crystals. The yield was 2.41 g (97%).
5 ¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.91-2.11 (2H, m), 2.61-2.68 (2H, m), 2.88-3.05 (2H, m), 3.08-3.26 (2H, m), 3.96 (2H, t, J=5.9 Hz), 4.25 (4H, br s), 7.13-7.38 (5H, m), 8.05-8.32 (3H, m).
IR (KBr): 2974, 1751, 170, 1379, 1261, 1165, 962, 760, 702 cm⁻¹.

10 Reference Example 58

Synthesis of 2-amino-6-fluoropyridine

A solution of 30.0 g of 2,6-difluoropyridine in 150 mL (4.6 equivalents) was stirred in a sealed tube (inner pressure 12.1 kgcm⁻²) for 5 hours at 130°C. The reaction mixture was cooled to 0°C, which was left standing for two hours. Resulting crude crystals (plates) were collected by filtration with a glass filter, which were dried at 40°C for 2 hours under reduced pressure (24.2 g, yield 82.6%).

20 ¹H-NMR (CDCl₃, 300 MHz) δ: 4.33-4.74 (2H, br s), 6.20 (1H, m), 6.30 (1H, m), 7.48 (1H, m).

Elemental analysis for C₅H₅N₂F

Calcd.: C, 53.57; H, 4.50; N, 24.97; F, 16.95

Found : C, 53.44; H, 4.45; N, 24.97; F, 17.25

25 Reference Example 59

Synthesis of 6-(2-fluoropyridinyl)thioacetic acid ethyl ester

To a solution of 2,6-difluoropyridine (5 mL) in DMF (10 mL) were added potassium carbonate (1 equivalent) and thioglycolic acid ethyl ester (1 equivalent). The mixture was stirred overnight at room temperature. To the reaction mixture were added ethyl acetate (100 mL × 3) and water (100 mL). The aqueous layer was subjected to extraction. The extract was combined with the ethyl acetate solution, which was washed with a saturated aqueous saline solution (100 mL

x 3), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford 6-(2-fluoropyridinyl)thioacetic acid ethyl ester (10 g, yield 84%) as an oily product.

5 ¹H-NMR (CDCl₃, 300 MHz) δ: 1.28 (3H, t, J = 7.1 Hz), 3.93 (2H, s), 4.22 (2H, q, J=7.1 Hz), 6.60 (1H, ddd, J=2.6, 7.9 & 7.9 Hz), 7.11 (1H, ddd, J=2.3, 7.9 & 7.9 Hz), 7.59 (1H, ddd, J=7.9, 7.9 & 7.9 Hz).

10 IR (neat): cm⁻¹.

Elemental analysis for C₂₉H₃₆Cl₂N₄OS·2.5H₂O

Calcd.: C, 57.61; H, 6.83; N, 9.27

Found : C, 57.56; H, 7.10; N, 8.88

Reference Example 60

15 Synthesis of 2-fluoro-6-(formylamino)pyridine

A solution of 0.63 g of 2,6-difluoropyridine in 0.2 mL of formamide was stirred for 3 hours at 150°C. The reaction mixture was cooled to room temperature, to which were added water (100 mL) and ethyl acetate (100 mL x 3) for extraction. The extract solution was dried over anhydrous magnesium sulfate, followed by concentration to give powdery precipitate of 2-fluoro-6-(formylamino)pyridine. The powdery product was collected by filtration and dried for 2 hours at 40°C under reduced pressure (0.4 g).

25 ¹H-NMR (CDCl₃, 300 MHz) δ: 6.64-6.73 (128/93H, m), 7.72-7.88 (1H, m), 8.11 (58/93H, m), 8.51 (58/93H, s), 8.77 (1H, br s), 9.32 (35/93H, d, J=10.6 Hz).

Reference Example 61

30 Synthesis of 5-fluoroimidazo[1,2-a]pyridine

2-Amino-6-fluoropyridine (12 g) was completely dissolved in 120 mL of distilled water at 60°C. To the solution was added 35 mL (2 equivalents) of 40% chloroacetaldehyde. The mixture was stirred for 3 hours at 60°C. The reaction mixture was gradually cooled to room temperature, to which were added a 1N-

HCl aqueous solution (50 mL) and ethyl acetate (150 mL). The ethyl acetate solution was subjected to extraction with a 1N-HCl aqueous solution (100 mL). The extract was mixed with the aqueous solution. To 5 this aqueous solution was added NaHCO₃ for neutralization (pH 0.35 ~ 7.30). To the neutralized aqueous solution was added a mixture of ethyl acetate and THF (4:1) (150 mL x 3) to extract the product. The extract solutions were combined and dried over 10 anhydrous magnesium sulfate, which was concentrated under reduced pressure to afford 5-fluoroimidazo[1,2-a]pyridine as a black liquid product (9.5 g, yield 65%).

15 ¹H-NMR (CDCl₃, 300 MHz) δ: 6.52 (1H, m), 7.26 (1H, m), 7.49 (2H, d, J=9.1 Hz), 7.66 (2H, m).

MS (SIMS), 137(MH⁺).

Reference Example 62

Synthesis of 5-fluoroimidazo[1,2-a]pyridine

20 2-Fluoro-6-formylaminopyridine (5 g) was dissolved in 50 mL of ethanol. To the solution was added 23.5 mL (e equivalents) of 40% chloroacetaldehyde. The mixture was stirred for one hour under reflux. The reaction mixture was gradually cooled to room temperature, to which were added a 1N-HCl aqueous solution (100 mL) and 25 ethyl acetate (100 mL). The ethyl acetate solution was subjected to extraction with a 1N-HCl aqueous solution (100 mL x 2). The aqueous solutions were combined, to which was added NaHCO₃ for neutralization (pH 0.35 ~ 7.30). To the neutralized aqueous solution was added 30 ethyl acetate (100 mL x 3) to extract the product. The extract solutions were combined and dried over magnesium sulfate, which was concentrated under reduced pressure to afford 5-fluoroimidazo[1,2-a]pyridine as a black liquid product (1.5 g, yield 31%).

35 Reference Example 63

Synthesis of 5-fluoroimidazo[1,2-a]pyridine mono-

hydrochloride

To the black liquid 5-fluoroimidazo[1,2-a]pyridine (650 mg) was added conc. hydrochloric acid (5 mL). The mixture was concentrated, which was crystallized from a mixture of ethanol, THF and ethyl acetate (10mL:50mL:200mL) to afford 5-fluoroimidazo[1,2-a]pyridine monohydrochloride as a powdery product (690 mg, yield 83%).
5
10 $^1\text{H-NMR}$ (D_2O , 300 MHz) δ : 7.24 (1H, m), 7.78 (1H, d, $J=9.1$ Hz), 7.98-8.10 (2H, m), 8.15 (1H, m).

Reference Example 64**Synthesis of (imidazo[1,2-a]pyridin-5-ylthio) ethyl acetate**

In 10 mL of dimethylformamide was dissolved 1.2 g of 5-fluoroimidazo[1,2-a]pyridine. To the solution were added 1.8 g of potassium carbonate and 1.5 mL of thioglycolic acid ethyl ester. The mixture was stirred for 4 hours at room temperature. To the reaction mixture were added a 1N-HCl aqueous solution (100 mL) and ethyl acetate (100 mL). The ethyl acetate solution was subjected to extraction with a 1N-HCl aqueous solution (100 mL x 2). The aqueous solutions were combined, to which was added NaHCO_3 to neutralize (pH 0.35 - 7.30). To the thus-neutralized aqueous solution was added ethyl acetate (100 mL x 3) to extract the product. These extract solutions were combined and washed with a saturated aqueous saline solution (100 mL x 3), which was dried over anhydrous magnesium sulfate, followed by concentration under reduced pressure to afford (imidazo[1,2-a]pyridin-5-ylthio) ethyl acetate as a black liquid product (1.7 g, 80%).
15
20
25
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35 $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 1.17 (3H, t, $J=7.2$ Hz), 3.68 (2H, s), 4.12 (2H, q, $J=7.2$ Hz), 7.07 (1H, dd, $J=1.0$ & 7.0 Hz), 7.16 (1H, dd, $J=7.0$ & 8.9 Hz), 7.65 (1H, d, $J=8.9$ Hz), 7.71 (1H, s), 7.91 (1H, s).

Reference Example 65

Synthesis of (imidazo[1,2-a]pyridin-5-ylthio) ethyl acetate from 5-chloroimidazo[1,2-a]pyridine monohydrochloride

In a 50 mL-capacity reaction vessel, 1 g of 5-chloroimidazo[1,2-a]pyridine monohydrochloride was suspended in 10 mL of dimethylformamide under argon atmosphere. To the reaction vessel was added 1.5 mL of triethylamine. The mixture was stirred for 15 minutes, to which was added 2.4 mL of thioglycolic acid ethyl ester. The mixture was stirred for 2 hours at 60°C and for further 2 hours at 80°C. The reaction mixture was left standing for cooling, to which were added a 1N-HCl aqueous solution (50 mL) and ethyl acetate (100 mL). The ethyl acetate layer was subjected to extraction with a 1N-HCl aqueous solution (50 mL x 2). The acid aqueous solutions were combined, to which was added NaHCO₃ to neutralize (pH 0.35 - 7.30). To the thus-neutralized aqueous solution was added ethyl acetate (50 mL x3) to extract the product. The extract solutions were combined, which was washed with a saturated aqueous saline solution (50 mL x 3), dried over anhydrous magnesium sulfate and subjected to filtration. The filtrate was concentrated under reduced pressure to afford (imidazo[1,2-a]pyridin-5-ylthio) ethyl acetate as a black liquid product (1.8 g, quantitative yield 62.1%, HPLC 87.5%).

Reference Example 66

Synthesis of (imidazo[1,2-a]pyridin-5-ylthio) ethyl acetate from 5-bromoimidazo[1,2-a]pyridine

In a 50 mL-capacity reaction vessel, 103.2 mg of 5-bromoimidazo[1,2-a]pyridine was dissolved in 1 mL of dimethylformamide under argon atmosphere. To the reaction vessel was added 0.11 mL of triethylamine, to which was added 0.085 mL of thioglycolic acid ethyl ester. The mixture was stirred for 1.5 hour at room

temperature, for 2 hours at 60°C and for 9 hours at 80°C. The reaction mixture was left standing for cooling, to which were added a 1N-HCl aqueous solution (50 ml) and ethyl acetate (100 mL). The ethyl acetate layer was subjected to extraction with a 1N-HCl aqueous solution (50 mL x 2). The acid aqueous solutions were combined, to which was added NaHCO₃, for neutralization (pH 0.35 - 7.30). To the thus-neutralized solution was added ethyl acetate (50 mL x 3) for extracting the product. The extract solutions were combined and dried over anhydrous magnesium sulfate, which was subjected to filtration. The filtrate was concentrated under reduced pressure to afford (imidazo[1,2-a]pyridin-5-ylthio) ethyl acetate as a black liquid product (150 mg, quantitative yield 56.9%, HPLC 79.1%).

Reference Example 67

Synthesis of 2-fluoro-6-methyl thiopyridine

To a solution of 2,6-difluoropyridine (1 g) in THF (10 mL) was added sodium thiomethoxide (731 mg, 1,2 equivalent) at 0°C under argon atmosphere. The mixture was stirred overnight. To the reaction mixture were added ethyl acetate (30 mL x 2) and water (30 mL) to conduct extraction from the aqueous layer. The ethyl acetate solutions were combined and washed with water (20 mL x 2), which was dried over anhydrous sodium sulfate, followed by filtration. The filtrate was concentrated under reduced pressure to afford 2-fluoro-6-methyl thiopyridine (1.09 g, yield 88%).
¹H-NMR (CDCl₃, 300 MHz) δ: 2.55 (3H, s), 3.93 (2H, s), 3.57 (1H, m), 7.05 (1H, m), 7.56 (1H, m).

Reference Example 68

Synthesis of 2-amino-6-methyl thiopyridine

In a sealed reaction vessel (inner pressure 12,1 kgcm⁻²), a solution of 900 mg of 2-fluoro-6-methyl thiopyridine in 5 mL of a 28% aqueous ammonia was stirred for one hour at 150°C and for 6 hours at 180°C.

The reaction mixture was cooled to room temperature, to which were added ethyl acetate (50 mL) and water (50 mL). The aqueous layer was subjected to extraction with ethyl acetate (50 mL). The ethyl acetate layers were combined and washed with water (50 mL x 2), which was dried over anhydrous sodium sulfate, followed by filtration. The filtrate was concentrated under reduced pressure to leave a yellow oily product. (crystallized by leaving standing overnight) (873 g, yield 99%).

¹H-NMR (CDCl₃, 300 MHz) δ: 2.49 (3H, s), 4.40 (2H, br s), 6.18 (1H, dd, J=0.5 & 8.1 Hz), 6.53 (1H, dd, J=0.5 & 7.7 Hz), 7.26 (1H, dd, J=7.7 & 8.1 Hz).

Reference Example 69

15 Synthesis of 2-amino-6-methyl thiopyridine

To 2-amino-6-fluoropyridine (300 mg) was added an aqueous solution of sodium thiomethoxide (13 ml, 10 equivalents). The suspension was stirred for one hour at 80°C and for 5 hours at 100°C. The reaction mixture was cooled to room temperature, to which were added ethyl acetate (40 mL x 2) and water (30 mL). The aqueous layer was subjected to extraction. Ethyl acetate solutions were combined and washed with water (40 mL), which was dried over anhydrous sodium sulfate, followed by filtration. The filtrate was concentrated under reduced pressure to give an oily product (crystallized by leaving standing overnight) (237 mg, yield 63%).

Reference Example 70

30 Synthesis of 5-methyl thioimidazo[1,2-a]pyridine

A solution of 3.094 g of 2-amino-6-methyl thiopyridine in 31 mL of ethanol was heated to 60°C. To the solution was added dropwise 14.6 mL of 40% chloroacetaldehyde. The mixture was stirred for one hour, which was cooled and concentration. To the concentrate was added 60 mL of 1N-HCl, which was washed

with ethyl acetate (20 mL x 2). To the aqueous layer was added 50 mL of 2N-sodium hydroxide, which was subjected to extraction with ethyl acetate (30 mL x 3). The ethyl acetate layers were combined and washed with water (20 mL x 2), which was dried over sodium sulfate, followed by filtration and concentration to afford 5.01 g of a brown oily product (yield 83.0%).
¹H-NMR (CDCl₃, 300 MHz) δ: 2.61 (3H, s), 6.76 (1H, m), 7.18 (1H, m), 7.55 (1H, m), 7.73 (2H, m).

10 Reference Example 71

Synthesis of imidazo[1,2-a]pyridine-5-thiol

A flask was charged, under argon atmosphere, 2 mL of xylene, 0.1 mL of hexamethyl phosphoric triamide and 24.4 mg of sodium hydride. The mixture was heated to 45°C, to which was added 0.06 mL of diethylamine. The mixture was stirred for 20 minutes, to which was added a solution of 57 mg of 5-methyl thioimidazo [1,2-a]pyridine in 1 mL of xylene. The mixture was heated to 150°C, which was stirred for 2.5 hours. The reaction mixture was cooled, to which were added 5 mL of water and 10 mL of 1N-HCl. The mixture was washed with 20 mL of ethyl acetate. The aqueous layer was adjusted to pH 8.5 with 2N-NaOH, which was subjected to extraction with ethyl acetate. The extract solution was dried over Na₂SO₄ which was subjected to filtration. The filtrate was concentrated to leave imidazo[1,2-a]pyridine-5-thiol (10 mg, 19%) as a brown oily product.

¹H-NMR (DMSO-d₆, 300 MHz) δ: 6.93 (2H, m), 7.30 (1H, m), 7.85 (1H, m), 8.32 (1H, m).

Reference Example 72

Synthesis of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid

To a solution of 120.02 g (0.7991 mol.) of imidazo[1,2-a]pyridine-5-thiol and 134 mL (0.959 mol.) of triethylamine in 500 mL ethanol was added dropwise,

at room temperature, 88.6 mL (0.799 mol.) of ethyl bromoacetate. The mixture was stirred for 2 hours at room temperature. The solvent of the reaction mixture was distilled off under reduced pressure. To the residue was added ethyl acetate, then resulting precipitate (principally triethylamine·hydrochloride) was collected by filtration and washed with ethyl acetate. The filtrate and the washing were combined, from which the solvent was distilled off to leave (imidazo[1,2-a]pyridin-5-ylthio) ethyl acetate as a crude product. This crude product was used for the subsequent reaction without purification.

Brown liquid product Yield 199.7 g

A solution of 199.7 g of the crude (imidazo[1,2-a]pyridin-5-ylthio) ethyl acetate and 224 g (1.60 mol.) of hexamethylene tetramine in 500 mL of acetic acid was stirred for one day at 90°C. The reaction mixture was poured into water, which was subjected to extraction twice with ethyl acetate. The organic layers were combined and washed with water, which was dried over anhydrous magnesium sulfate, followed by distilling off the solvent under reduced pressure to leave a solid matter. The solid matter was washed with diethyl ether to give ethyl 5-thia-1,8b-diazaacenaphthylene-4-carboxylate as a crude product. This crude product was used for the subsequent reaction without purification.

Blackish purple solid product Yield 193.69 g

To a solution of 193.69 g of ethyl 5-thia-1,8b-diazaacenaphthylene-4-carboxylate in 1 liter of ethanol was added a solution of 62.9 g (1.57 mol.) of sodium hydroxide in 50 mL of water. The mixture was stirred for 0.5 hour at room temperature. To the reaction mixture was added about 130 mL of conc. hydrochloric acid while stirring until the pH became about 4-5. The resulting precipitate was collected by filtration, which was washed with ethanol, acetone and diethyl

ether successively to give 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid.
Orange solid Yield 96.3 g (55%)
 $^1\text{H-NMR}$ (DMSO-d₆, 200 MHz) δ: 5.97 (1H, dd, J=6.6 & 1.2
5 Hz), 6.57-6.73 (2H, m), 6.88 (1H, s), 7.12 (1H, s).

Reference Example 73

Synthesis of 4-amino-1-(3-phenylpropyl)piperidine
5%-Palladium/carbon(2.5 g) and 28%-sodium
10 methoxide (32.9 g) were added into the methanol
solution (467 mL) of 1-(3-phenylpropyl)-4-
aminopyridinium bromide (50 g). The mixture was
subjected by catalytic reduction for 5 hours under
hydrogen pressure (6-8 atm) and at 40°C. After this
15 mixture was cooled, the filtrate removed the catalyst
was concentrated. Ethyl acetate (1L) and water (200
mL), and further 2N-sodium hydroxide with cooling with
ice were added into the concentrated solution. The
separate solution was washed with water (300 mL), dried
20 over sodium sulfate, and concentrated.

Acetonitrile (476 mL), and 3.5N-hydrochloric
acid/ethyl acetate (195 mL) with cooling with ice were
added into the concentrated solution. After stirring
for 40 minutes at room temperature, the mixture was
25 filtrated, and washed with acetonitrile (70 mL). This
was dried under reduced pressure to obtain 4-amino-1-
(3-phenylpropyl)piperidine 2 hydrochloride (42.86,
86.3%).

$^1\text{H-NMR}$ (D₂O, 300MHz) δ: 1.7-2.0 (m, 6H), 2.5 (t, 2H,
30 J=7.5 Hz), 2.8-3.2 (m, 4H), 3.3-3.6 (m, 3H), 7.1-
7.3 (m, 5H).

Reference Example 74

Synthesis of 4-amino-1-(3-phenylpropyl)piperidine
The mixture of 1-(3-phenylpropyl)-4-
35 aminopyridinium bromide (10 g), 2-propanol (200 mL),
sodium methoxide (1.84 g) and sodium borohydride (10 g)

were refluxed under heating. Methanol (50 mL) was added dropwise to the mixture per 30 minutes. The solution was refluxed for 2 hours, cooled to room temperature, and water (150 mL) and concentrated
5 hydrochloric acid (35 mL) were added into this. The mixture was stirred for 1.5 hours at room temperature. After adding 30%-sodium hydroxide (50 mL), the solution was concentrated. The concentrated solution was extracted by ethyl acetate (100 mL x 3), washed with
10 water (50 mL x 2), dried over sodium sulfate, filtered, and concentrated. This was dissolved in methanol-denatured alcohol (23 mL) with cooling with ice.
3.96N-Hydrochloric acid/methanol-denatured alcohol (15 mL) was added dropwise to this solution. This was
15 stirred for 30 minutes with cooling with ice, and stirred for 1 hour at room temperature. After dropping diisopropyl ether (60 mL), the solution was stirred for 2 hours at room temperature, and stirred for 1 hour with cooling with ice. The crystal filtered under
20 reduced pressure was washed with isopropyl ether (20 mL x 2). This was dried under reduced pressure to obtain 4-amino-1-(3-phenylpropyl)piperidine 2 hydrochloride (8.54 g, 86%).
¹H-NMR (D₂O, 300 MHz) δ: 1.7-2.0 (m, 6H), 2.5 (t, 2H,
25 J=7.5 Hz), 2.8-3.2 (m, 4H), 3.3-3.6 (m, 3H), 7.1-7.3 (m, 5H).

Reference Example 75

Synthesis of 1-(3-Aminopropan-1-yl)-4-tert-butoxycarbonyl-2-oxopiperazine

30 1) Synthesis of 4-tert-Butoxycarbonyl-2-oxopiperazine
Di-tert-butyl dicarbonate (10.4 g, 47.6 mmol) was added to a stirred solution of 2-oxopiperazine (4.77 g, 47.6 mmol) in ethanol (100 ml) at room temperature. After stirring at room temperature for 1 hour, the
35 reaction mixture was concentrated in vacuo to give 4-tert-butoxycarbonyl-2-oxopiperazine as colorless

crystals (8.00 g, 84%), which were collected by filtration and washed with hexane.

¹H-NMR (200 MHz, CDCl₃) δ: 6.90-6.56 (1H, m), 4.09 (2H, s), 3.64 (2H, t, J=5.2 Hz), 3.44-3.34 (2H, m), 1.48 (9H, s).

5 IR (KBr) : 3265, 3195, 2981, 1691, 1666, 1635, 1419, 1398, 1365, 1338, 1243, 1176, 1131, 1002 cm⁻¹.

2) Synthesis of 4-tert-Butoxycarbonyl-1-(3-phthalimidopropan-1-yl)-2-oxopiperazine

10 Sodium hydride (60% in oil, 1.78 g, 44.5 mmol) was added in a small portions to a stirred solution of 4-tert-butoxycarbonyl-2-oxopiperazine (8.00 g, 40.0 mmol) in N, N-dimethylformamide (100 ml) at room temperature and the mixture was stirred at room temperature for 1 hour. Then, N-(3-bromopropyl)phthalimide (12.5 g, 46.6 mmol) was added to the mixture. After stirring at room temperature for 1 hour, the reaction mixture was poured into water and extracted with ethyl acetate. The extract was successively washed with water, brine, dried over MgSO₄ and concentrated in vacuo. The residue was chromatographed on silica gel (150 g) with hexane-ethyl acetate (1:1) to give 4-tert-butoxycarbonyl-1-(3-phthalimidopropan-1-yl)-2-oxopiperazine as a colorless oil (9.02 g, 55%).

25 ¹H-NMR (200 MHz, CDCl₃) δ: 7.90-7.80 (2H, m), 7.80-7.68 (2H, m), 4.07 (2H, s), 3.72 (2H, t, J=5.2 Hz), 3.67 (2H, t, J=5.2 Hz), 3.50 (2H, t, J=7.2 Hz), 3.37 (2H, t, J=5.2 Hz), 1.98 (2H, tt, J=7.2 and 7.2 Hz), 1.47 (9H, s).

30 IR (neat) : 2976, 2935, 1772, 1714, 1652, 1398, 1367, 1239, 1170, 1126, 722 cm⁻¹.

3) Synthesis of 1-(3-Aminopropan-1-yl)-4-tert-butoxycarbonyl-2-oxopiperazine

35 Hydrazine monohydrate (1.75 g, 46.6 mmol) was added to a stirred solution of 4-tert-butoxycarbonyl-1-(3-phthalimidopropan-1-yl)-2-oxopiperazine (9.02 g,

23.3 mmol) in ethanol (50 ml) at room temperature. The reaction mixture was refluxed for 1 hour. The precipitates were removed off by filtration and the filtrate was concentrated in vacuo. The residue was dissolved in 2N-sodium hydroxide and extracted with chloroform. The extract was washed with brine, dried over MgSO₄ and concentrated in vacuo to give 1-(3-aminopropan-1-yl)-4-tert-butoxycarbonyl-2-oxopiperazine as a colorless oil (5.43 g, 91%).

10 ¹H-NMR (200 MHz, CDCl₃) δ: 4.29 (2H, m), 4.07 (2H, s), 3.69-3.60 (2H, m), 3.51-3.20 (4H, m), 2.71 (2H, t, J=7.0 Hz), 2.03-1.92 (2H, m), 1.47 (9H, s).
IR (neat) : 2977, 1695, 1652, 1419, 1367, 1326, 1247, 1168 cm⁻¹.

15 Reference Example 76
 Synthesis of 3-(4-tert-Butoxycarbonylaminophenyl)propyl methanesulfonate
1) Synthesis of (E)-Ethyl 3-(4-Nitrophenyl)acrylate
Sodium hydride (60% in oil, 2.22 g, 55.5 mmol) was added to a stirred solution of 4-nitrobenzaldehyde (8.00 g, 52.9 mmol) and triethyl phosphonoacetate (12.4 g, 55.5 mmol) in N,N-dimethylformamide (50 ml) at 0°C. After stirring at 0°C for 30 minutes, the reaction mixture was poured into water to give (E)-ethyl 3-(4-nitrophenyl)acrylate as colorless crystals (11.7 g, quant.), which were collected by filtration and successively washed with water and hexane.
mp 133-135°C.
1H-NMR (200 MHz, CDCl₃) δ: 8.26 (2H, d, J=8.8 Hz), 7.72 (1H, d, J=16.0 Hz), 7.68 (2H, d, J=8.8 Hz), 6.57 (1H, d, J=16.0 Hz), 4.30 (2H, q, J=7.0 Hz), 1.36 (3H, t, J=7.0 Hz).
IR (KBr) : 3107, 3080, 2985, 2908, 1714, 1646, 1594, 1517, 1342, 1313, 1180, 979, 844 cm⁻¹.
2) Synthesis of Ethyl 3-(4-Aminophenyl)propionate
(E)-Ethyl 3-(4-nitrophenyl)acrylate (11.7 g, 52.9

mmol) in tetrahydrofuran (100 ml) was hydrogenated over 10% Palladium-Carbon (1.20 g) at atmospheric pressure. After removal of the catalyst, the filtrate was concentrated in vacuo to give ethyl 3-(4-aminophenyl)propionate as a yellow oil (9.66 g, 95%).

5 $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 6.99 (2H, d, $J=8.4$ Hz), 6.62 (2H, d, $J=8.4$ Hz), 4.12 (2H, q, $J=7.0$ Hz), 3.60-3.00 (2H, m), 2.84 (2H, t, $J=7.6$ Hz), 2.55 (2H, t, $J=7.6$ Hz), 1.23 (3H, t, $J=7.0$ Hz).

10 IR (neat) : 3371, 2981, 2925, 1729, 1627, 1519, 1372, 1282, 1180, 1155, 1037, 825 cm^{-1} .

3) Synthesis of Ethyl 3-(4-tert-butoxycarbonylaminophenyl)propionate

A mixture of ethyl 3-(4-aminophenyl)propionate (9.66 g, 50.0 mmol), di-tert-butyl dicarbonate (13.1 g, 60.0 mmol), triethylamine (6.07 g, 60.0 mmol) and tetrahydrofuran (50 ml) was stirred at room temperature for 17 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The extract

15 was successively washed with water and brine, dried over MgSO_4 and concentrated in vacuo. The residue was chromatographed on silica gel (150 g) with hexane-ethyl acetate (5:1) to give ethyl 3-(4-tert-butoxycarbonylaminophenyl)propionate as a yellow oil

20 (14.7 g, quant.).

25 $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 7.27 (2H, d, $J=8.6$ Hz), 7.12 (2H, d, $J=8.6$ Hz), 6.42 (1H, brs), 4.12 (2H, q, $J=7.0$ Hz), 2.90 (2H, t, $J=8.0$ Hz), 2.58 (2H, t, $J=8.0$ Hz), 1.53 (9H, s), 1.23 (3H, t, $J=7.0$ Hz).

30 IR (neat) : 3344, 2981, 1808, 1729, 1527, 1372, 1315, 1215, 1160, 1118, 1072 cm^{-1} .

4) Synthesis of 3-(4-tert-Butoxycarbonylaminophenyl)propanol

Diisobutylaluminium hydride(1.5 M in toluene, 30.5 ml, 45.8 mmol) was added dropwise to a stirred solution of ethyl 3-(4-tert-butoxycarbonylaminophenyl)propionate

(6.10 g, 20.8 mmol) in tetrahydrofuran (60 ml) at 0°C and the mixture was stirred at 0°C for 1 hour. 2N-hydrochloric acid was added to the mixture and the mixture was extracted with ethyl acetate. The extract 5 was successively washed with water, saturated aqueous NaHCO₃, and brine, dried over MgSO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (100 g) with hexane-ethyl acetate (3:2) to give 3-(4-tert-butoxycarbonylaminophenyl)propanol as a colorless 10 oil (2.66 g, 51%).

¹H-NMR (200 MHz, CDCl₃) δ: 7.34-7.00 (4H, m), 6.44 (1H, brs), 3.67 (2H, t, J=6.4 Hz), 2.80-2.60 (2H, m), 2.00-1.80 (2H, m), 1.43 (9H, s).
IR (neat) : 3311, 2979, 2933, 1726, 1521, 1369, 1243, 15 1158, 1116, 1054 cm⁻¹.

5) Synthesis of 3-(4-tert-Butoxycarbonylaminophenyl)propyl methanesulfonate
A mixture of 3-(4-tert-butoxycarbonylaminophenyl)propanol (2.66 g, 10.6 mmol), 20 methanesulfonylchloride (1.33 g, 11.6 mmol), triethylamine (1.18 g, 11.7 mmol) and ethyl acetate (10 ml) was stirred at room temperature for 1 hour. Then the reaction mixture was diluted with ethyl acetate and successively washed with water and brine, dried over 25 MgSO₄ and concentrated in vacuo. The residue was chromatographed on silica gel (50 g) with hexane-ethyl acetate (3:1) to give 3-(4-tert-butoxycarbonylaminophenyl)propyl methanesulfonate as colorless crystals (2.75 g, 79%).

30 ¹H-NMR (200 MHz, CDCl₃) δ: 7.35-7.00 (4H, m), 6.44 (1H, brs), 4.21 (2H, t, J=6.4 Hz), 2.99 (3H, s), 2.70 (2H, t, J=7.4 Hz), 2.15-1.95 (2H, m), 1.52 (9H, s).

35 IR (KBr) : 3381, 2979, 1706, 1529, 1349, 1237, 1168, 952 cm⁻¹.

Reference Example 77

Synthesis of 3-(3-tert-Butoxycarbonylaminophenyl)propyl Methanesulfonate

1) Synthesis of (E)-Ethyl 3-(3-Nitrophenyl)acrylate

Sodium hydride (60% in oil, 2.22 g, 55.5 mmol) was added to a stirred solution of 3-nitrobenzaldehyde (8.00 g, 52.9 mmol) and triethyl phosphonoacetate (12.4 g, 55.5 mmol) in N,N-dimethylformamide (50 ml) at 0°C. After stirring at 0°C for 1.5 hours, the reaction mixture was poured into water to give (E)-ethyl 3-(3-nitrophenyl)acrylate as colorless crystals (11.7 g, quant.), which were collected by filtration and washed with water and hexane.

mp 65-66°C.

¹H-NMR (200 MHz, CDCl₃) δ: 8.42-8.35 (1H, m), 8.24 (1H, dd, J=8.0 and 2.2 Hz), 7.88-7.80 (1H, m), 7.73 (1H, d, J=15.6 Hz), 7.59 (1H, dd, J=8.0 and 8.0 Hz), 6.57 (1H, d, J=15.6 Hz), 4.30 (2H, q, J=6.0 Hz), 1.36 (3H, t, J=6.0 Hz).

2) Synthesis of Ethyl 3-(3-Aminophenyl)propionate
(E)-Ethyl 3-(3-nitrophenyl)acrylate (12.1 g, 52.9 mmol) in tetrahydrofuran (100 ml) was hydrogenated over 10% palladium-Carbon (2.80 g) at atmospheric pressure. After removal of the catalyst, the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (100 g) with hexane-ethyl acetate (3:1) to give ethyl 3-(3-aminophenyl)propionate as a yellow oil (6.21 g, 61%).

¹H-NMR (200 MHz, CDCl₃) δ: 7.12-7.00 (1H, m), 6.65-6.50 (3H, m), 4.13 (2H, q, J=7.0 Hz), 3.62 (2H, brs), 2.86 (2H, t, J=7.0 Hz), 2.58 (2H, t, J=7.0 Hz), 1.24 (3H, t, J=7.0 Hz).

3) Synthesis of Ethyl 3-(3-tert-butoxycarbonylaminophenyl)propionate
A mixture of ethyl 3-(3-aminophenyl)propionate (6.21 g, 32.1 mmol), di-tert-butyl dicarbonate (8.41g, 38.5 mmol), triethylamine (3.90 g, 38.5 mmol) and

tetrahydrofuran (30 ml) was stirred at room temperature for 19 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was successively washed with water and brine, dried over MgSO₄ and concentrated in vacuo. The residue was chromatographed on silica gel (100 g) with hexane-ethyl acetate (8:1) to give ethyl 3-(3-tert-butoxycarbonylaminophenyl)propionate as a yellow oil (9.35 g, 99%).

10 ¹H-NMR (200 MHz, CDCl₃) δ: 7.40-7.10 (3H, m), 6.90-6.80 (1H, m), 6.44 (1H, brs), 4.13 (2H, q, J=7.2 Hz), 2.92 (2H, t, J=7.8 Hz), 2.60 (2H, t, J=7.8 Hz), 1.51 (9H, s), 1.24 (3H, t, J=7.2 Hz).
IR (neat) : 3346, 2981, 2933, 1733, 1612, 1594, 1538, 1494, 1442, 1369, 1236, 1162, 1056, 871, 788 cm⁻¹.

15 4) Synthesis of 3-(3-tert-Butoxycarbonylaminophenyl)propanol

20 Diisobutylaluminium hydride (1.5 M in toluene, 57.0 ml, 85.5 mmol) was added dropwise to a stirred solution of ethyl 3-(3-tert-butoxycarbonylaminophenyl)propionate (9.35 g, 31.9 mmol) in tetrahydrofuran (100 ml) at 0°C and the mixture was stirred at room temperature for 24 hours. 2N-hydrochloric acid was added to the mixture and the 25 mixture was extracted with ethyl acetate. The extract was successively washed with water saturated aqueous NaHCO₃ and brine, dried over MgSO₄ and concentrated in vacuo. The residue was chromatographed on silica gel (100 g) with hexane-ethyl acetate (2:1) to give 3-(3-tert-butoxycarbonylaminophenyl)propanol as a colorless 30 oil (3.24 g, 40%).

35 ¹H-NMR (200 MHz, CDCl₃) δ: 7.30-7.05 (3H, m), 7.00-6.80 (1H, m), 6.47 (1H, brs), 3.66 (2H, t, J=6.4 Hz), 2.68 (2H, t, J=7.6 Hz), 2.00-1.80 (2H, m), 1.52 (9H, s).
IR (neat) : 3317, 2979, 2933, 1699, 1610, 1592, 1538,

1490, 1442, 1369, 1245, 1160, 1056, 778 cm⁻¹.

5) Synthesis of 3-(3-tert-Butoxycarbonylaminophenyl)propyl Methanesulfonate

A mixture of 3-(3-tert-butoxycarbonylaminophenyl)propanol (3.24 g, 12.9 mmol), methanesulfonylchloride (1.63 g, 14.2 mmol), triethylamine (1.44 g, 14.2 mmol) and ethyl acetate (50 ml) was stirred at room temperature for 1 hour. Then the reaction mixture was diluted with ethyl acetate and successively washed with water and brine, dried over MgSO₄ and concentrated in vacuo. The residue was chromatographed on silica gel (50 g) with hexane-ethyl acetate (3:1) to give 3-(3-tert-butoxycarbonylaminophenyl)propyl methanesulfonate as a colorless oil (3.50 g, 82%).

¹H-NMR (200 MHz, CDCl₃) δ: 7.40-7.00 (3H, m), 6.86 (1H, d, J=6.6 Hz), 6.46 (1H, brs), 4.22 (2H, t, J=6.0 Hz), 3.01 (3H, s), 2.73 (2H, t, J=7.6 Hz), 2.20-1.98 (2H, m), 1.51 (9H, s).

20 Reference Example 78

Synthesis of 3-(4-Cyanophenyl)propyl Methanesulfonate

1) Synthesis of (E)-Ethyl 3-(4-Cyanophenyl)acrylate

Sodium hydride (60% in oil, 3.20 g, 80.0 mmol) was added to a stirred solution of 4-cyanobenzaldehyde (10.0 g, 76.3 mmol) and triethyl phosphonoacetate (18.0 g, 80.1 mmol) in N,N-dimethylformamide (80 ml) at 0°C. After stirring at 0°C for 1 hour, the reaction mixture was poured into water to give (E)-ethyl 3-(4-cyanophenyl)acrylate as colorless crystals (13.9 g, 91%), which were collected by filtration and washed with water and hexane.

¹H-NMR (200 MHz, CDCl₃) δ: 7.74-7.54 (4H, m), 7.63 (1H, d, J=16.2 Hz), 6.52 (1H, d, J=16.2 Hz), 4.29 (2H, q, J=7.0 Hz), 1.34 (3H, t, J=7.0 Hz).

IR (KBr) : 3402, 2987, 2227, 1706, 1641, 1560, 1473,

1369, 1166, 1002, 850 cm⁻¹.

2) Synthesis of Ethyl 3-(4-Cyanophenyl)propionate

(E)-Ethyl 3-(4-cyanophenyl)acrylate (13.9 g, 69.1 mmol) in tetrahydrofuran (100 ml) was hydrogenated over 10% Palladium-Carbon (4.00 g) at atmospheric pressure. After removal of the catalyst, the filtrate was concentrated in vacuo to give ethyl 3-(4-cyanophenyl)propionate as a yellow oil (13.7 g, 98%).
¹H-NMR (200 MHz, CDCl₃) δ: 7.59 (2H, d, J=8.2 Hz), 7.33 (2H, d, J=8.2 Hz), 4.13 (2H, q, J=7.0 Hz), 3.01 (2H, t, J=7.6 Hz), 2.64 (2H, t, J=7.6 Hz), 1.23 (3H, t, J=7.0 Hz).

IR (neat) : 2981, 2933, 2229, 1733, 1608, 1506, 1446, 1417, 1374, 1297, 1185, 1041, 827 cm⁻¹.

15 3) Synthesis of 3-(4-Cyanophenyl)propionic Acid

A mixture of ethyl 3-(4-cyanophenyl)propionate (6.00 g, 29.5 mmol), 2N-sodium hydroxide (30 ml, 60.0 mmol) and ethanol (60 ml) was stirred at room temperature for 1 hour. The reaction mixture was acidified with 1N-hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over MgSO₄, and concentrated in vacuo to give 3-(4-cyanophenyl)propionic acid as colorless crystals (4.40 g, 85%).

25 ¹H-NMR (200 MHz, CDCl₃) δ: 7.60 (2H, d, J=8.0 Hz), 7.33 (2H, d, J=8.0 Hz), 3.02 (2H, t, J=7.6 Hz), 2.71 (2H, t, J=7.6 Hz).

IR (KBr) : 3060, 2922, 2227, 1710, 1608, 1434, 1411, 1330, 1309, 1224, 935, 840 cm⁻¹.

30 4) Synthesis of 3-(4-Cyanophenyl)propanol

Borane-tetrahydrofuran complex (1.0 M in tetrahydrofuran, 33.0 ml, 33.0 mmol) was added dropwise to a stirred solution of 3-(4-cyanophenyl)propionic acid (4.40 g, 25.1 mmol) in tetrahydrofuran (50 ml) at 0°C and the stirring was continued at room temperature for 14 hours. Water (50 ml) and potassium carbonate

(10.0 g, 72.4 mmol) was added to the mixture. The mixture was extracted with ethyl acetate and the extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give 3-(4-cyanophenyl)propanol
5 as a yellow oil (3.20 g, 79%).

1H -NMR (200 MHz, $CDCl_3$) δ : 7.58 (2H, d, $J=8.2$ Hz), 7.31 (2H, d, $J=8.2$ Hz), 3.68 (2H, t, $J=6.2$ Hz), 2.79 (2H, t, $J=7.8$ Hz), 2.00-1.75 (2H, m).
IR (neat) : 3319, 2943, 2229, 1608, 1505, 1415, 1054,
10 854, 817 cm^{-1} .

5) Synthesis of 3-(4-Cyanophenyl)propyl Methanesulfonate
A mixture of 3-(4-cyanophenyl)propanol (3.77 g, 23.4 mmol), methanesulfonylchloride (2.96 g, 25.8 mmol), triethylamine (2.60 g, 25.7 mmol) and ethyl acetate (100 ml) was stirred at room temperature for 30 minutes. Then the reaction mixture was diluted with ethyl acetate and successively washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (60 g) with hexane-ethyl acetate (1:1) to give 3-(4-cyanophenyl)propane methanesulfonate as a colorless oil (4.79 g, 86%).

1H -NMR (200 MHz, $CDCl_3$) δ : 7.61 (2H, d, $J=8.4$ Hz), 7.31 (2H, d, $J=8.4$ Hz), 4.24 (2H, t, $J=6.2$ Hz), 3.02 (3H, s), 2.83 (2H, t, $J=7.8$ Hz), 2.09 (2H, tt, $J=7.8$ and 6.2 Hz).
IR (neat) : 3028, 2941, 2227, 1608, 1506, 1351, 1172, 975, 929, 836, 815 cm^{-1} .

Reference Example 79
30 Synthesis of 4-(3-Aminopropan-1-yl)-1-(3-phenylpropan-1-yl)-2-oxopiperazine
1) Synthesis of 4-tert-Butoxycarbonyl-1-(3-phenylpropan-1-yl)-2-oxopiperazine
Sodium hydride (60% in oil, 630 mg, 15.8 mmol) was
35 added to a stirred solution of 4-tert-butoxycarbonyl-2-oxopiperazine (3.00 g, 15.0 mmol) in N, N-

dimethylformamide (40 ml) at room temperature and the stirring was continued at room temperature for 30 minutes. 1-Bromo-3-phenylpropane (3.29 g, 16.5 mmol) was added to the mixture and the stirring was continued at room temperature for 1 hour. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was successively washed with water, brine, dried over MgSO₄ and concentrated in vacuo. The residue was chromatographed on silica gel (50 g) with hexane-ethyl acetate (1:1) to give 4-tert-butoxycarbonyl-1-(3-phenylpropan-1-yl)-2-oxopiperazine as colorless crystals (3.85 g, 81%), which were collected by filtration and washed with hexane.

10 ¹H-NMR (200 MHz, CDCl₃) δ: 7.35-7.15 (5H, m), 4.04 (2H, s), 3.57 (2H, t, J=5.4 Hz), 3.46 (2H, t, J=7.2 Hz), 3.28 (2H, t, J=5.4 Hz), 2.65 (2H, t, J=7.2 Hz), 1.90 (2H, tt, J=7.2 and 7.2 Hz), 1.46 (9H, s).

15 IR (KBr) : 2975, 2916, 1699, 1656, 1419, 1367, 1239, 1170, 1128, 992, 701 cm⁻¹.

20 2) Synthesis of 1-(3-Phenylpropan-1-yl)-2-oxopiperazine Concentrated hydrochloric acid (4.2 ml) was added to 4-tert-butoxycarbonyl-1-(3-phenylpropan-1-yl)-2-oxopiperazine (3.85 g, 12.1 mmol) at room temperature and the mixture was stirred at room temperature for 1 hour. The reaction mixture was basified with 8N-sodium hydroxide and extracted with ethyl acetate. The extract was washed with brine, dried over MgSO₄ and concentrated in vacuo to give 1-(3-phenylpropan-1-yl)-2-oxopiperazine as a colorless oil (2.49 g, 94%).

25 ¹H-NMR (200 MHz, CDCl₃) δ: 7.30-7.05 (5H, m), 3.48 (2H, s), 3.44 (2H, t, J=7.6 Hz), 3.25 (2H, t, J=5.4 Hz), 3.01 (2H, t, J=5.4 Hz), 2.65 (2H, t, J=7.6 Hz), 1.91 (2H, tt, J=7.6 and 7.6 Hz).

30 IR (neat) : 3290, 2927, 1635, 1496, 1454, 1344, 1315, 751, 701 cm⁻¹.

3) Synthesis of 1-(3-Phenylpropan-1-yl)-4-(3-phthaloylpropan-1-yl)-2-oxopiperazine

A mixture of 1-(3-phenylpropan-1-yl)-2-oxopiperazine (2.49 g, 11.4 mmol), N-(3-

5 bromopropyl)phthalimide (3.67 g, 13.7 mmol), potassium carbonate (1.89 g, 13.7 mmol) and N, N-dimethylformamide (20 ml) was stirred at room temperature for 4 hours. The reaction mixture was poured into water and extracted with ethyl acetate.

10 The extract was successively washed with water, brine, dried over MgSO₄ and concentrated in vacuo. The residue was chromatographed on silica gel (60 g) with hexane-ethyl acetate (1:4) to give 1-(3-phenylpropan-1-yl)-4-(3-phthaloylpropan-1-yl)-2-oxopiperazine as a

15 colorless oil (2.05 g, 44%).

¹H-NMR (200 MHz, CDCl₃) δ: 7.82 (2H, dd, J=5.2 and 3.2 Hz), 7.64 (2H, dd, J=5.2 and 3.2 Hz), 7.35-7.10 (5H, m), 3.77 (2H, t, J=6.6 Hz), 3.30 (2H, t, J=7.6 Hz), 3.16 (2H, t, J=5.4 Hz), 3.07 (2H, s), 2.70-2.52 (4H, m), 2.45 (2H, t, J=6.6 Hz), 2.00-1.70 (4H, m).

4) Synthesis of 4-(3-Aminopropan-1-yl)-1-(3-phenylpropan-1-yl)-2-oxopiperazine

Hydrazine monohydrate (382 mg, 7.63 mmol) was added to a stirred solution of 1-(3-phenylpropan-1-yl)-4-(3-phthaloylpropan-1-yl)-2-oxopiperazine (2.05 g, 5.05 mmol) in ethanol (10 ml) at room temperature. The reaction mixture was refluxed for 1 hour. The precipitates were removed off by filtration and the filtrate was concentrated in vacuo. The residue was dissolved in 2N-sodium hydroxide and extracted with chloroform. The extract was washed with brine, dried over MgSO₄ and concentrated in vacuo to give 4-(3-aminopropan-1-yl)-1-(3-phenylpropan-1-yl)-2-oxopiperazine as a colorless oil (1.38 g, 99%).

35 ¹H-NMR (200 MHz, CDCl₃) δ: 7.35-7.15 (5H, m), 3.43 (2H, t, J=7.6 Hz), 3.30 (2H, t, J=5.4 Hz), 3.13 (2H, s),

2.78 (2H, t, J=6.8 Hz), 2.71-2.58 (4H, m), 2.46 (2H, t, J=7.2 Hz), 2.05-1.75 (2H, m), 1.65 (2H, tt, J=6.8 and 6.8 Hz).

Example 1

5 **Synthesis of (R)-N-[1-(1,4-benzodioxan-2-ylmethyl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride**

1) **Synthesis of ethyl imidazo[1,2-a]pyridin-5-ylthio-acetate**

10 To a solution of 100.55 g (669.4 mM) of imidazo[1,2-a]pyridine-5-thiol and 112 ml (803 mM) of triethylamine in 500 ml of ethanol was added 81.7 ml (736 mM) of ethyl bromoacetate at room temperature and the mixture was stirred at room temperature for 2
15 hours. The solvent was then distilled off under reduced pressure and ethyl acetate was added to the residue. The resulting precipitate (triethylamine hydrochloride) was filtered off and washed with ethyl acetate. The filtrate and washes were pooled, the
20 solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate = 1:1 to ethyl acetate) to provide the title compound.

Brown liquid. Yield 132.34 g (84%)

25 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.169 (3H, t, 7.1 Hz), 3.678 (2H, s), 4.122 (2H, q, 7.1 Hz), 7.066 (1H, dd, 1.5 Hz, 6.9 Hz), 7.160 (1H, dd, 7.0 Hz, 8.8 Hz), 7.642 (1H, ddd, 0.7 Hz, 1.5 Hz, 8.8 Hz), 7.724 (1H, d, 1.0 Hz), 7.919 (1H, d, 0.6 Hz).

30 IR (neat): 3390, 2983, 1734, 1487, 1294, 1180, 1147, 1026, 783, 739 cm⁻¹.

2) **Synthesis of ethyl 5-thia-1,8b-diazaacenaphthylene-4-carboxylate**

Process A

35 To 250 ml of N,N-dimethylformamide was added 93.2 ml (1.0 M) of phosphorus oxychloride dropwise at 0°C

with constant stirring over 10 minutes and the mixture was further stirred at 0°C for 1 hour. To this solution was added a solution of 47.26 g (0.2 M) of ethyl imidazo[1,2-a]pyridin-5-ylthioacetate in 50 ml of N,N-dimethylformamide over 5 minutes and the mixture was stirred at 80°C for 16 hours. This reaction mixture was then poured in 1 l of iced water and, after thorough stirring, 1 l of ethyl acetate was added. To this mixture was added 50% aqueous solution of sodium hydroxide with ice-cooling and stirring until the aqueous layer had become neutral. The organic layer was washed with three 500 ml portions of water and further with 500 ml of saturated aqueous solution of sodium chloride and dried over MgSO₄. The solvent was then distilled off under reduced pressure to provide a deep-purple residue. This residue was rinsed with 250 ml of diethyl ether to provide the title compound as crude product. This crude product was not further purified but used as it was in the next reaction 3). Deep-purple solid. Yield 11.58 g (23.5%).
¹H-NMR (CDCl₃, 200 MHz) δ: 1.299 (3H, t, 7.1 Hz), 4.224 (2H, q, 7.1 Hz), 5.629-5.731 (1H, m), 6.506-6.609 (2H, m), 6.807 (1H, s), 7.006 (1H, s).
IR (nujol): 1693, 1614, 1267, 1227, 1043, 773, 735 cm⁻¹.

25 Process B

A 60% suspension of sodium hydride in liquid paraffin, 22.4 g (560 mM), was washed with two 100 ml portions of hexane followed by addition of 60 ml of N,N-dimethylformamide and the mixture was suspended in 500 ml of tetrahydrofuran. With the reaction vessel being cooled on a water bath, a solution of 132.34 g (560.1 mM) of ethyl imidazo[1,2-a]pyridin-5-ylthioacetate in 200 ml of tetrahydrofuran was added dropwise at room temperature and the mixture was stirred at the prevailing temperature for 2 hours. Then, on a water bath, 67.9 ml (840 mM) of ethyl

formate was added and the mixture was stirred at the prevailing temperature overnight. The resulting precipitate was recovered by filtration, washed serially with ethyl acetate and diethyl ether, and 5 dried to provide ethyl 2-(imidazo[1,2-a]pyridin-5-ylthio)-3-oxo-2-sodiopropionate. Yellow solid. Yield 114.37 g (71%).
¹H-NMR (CD₃OD, 200 MHz) δ: 1.222 (3H, t, 7.1 Hz), 4.119 (2H, q, 7.1 Hz), 6.676 (1H, d, 6.6 Hz), 7.207 (1H, dd, 7.0 Hz, 8.8 Hz), 7.291 (1H, d, 8.4 Hz), 7.590 (1H, s), 7.933 (1H, s), 9.400 (1H, s).
IR (nujol): 1662, 1558, 1273, 1065, 771, 732, 692 cm⁻¹.
Elemental analysis for C₁₂H₁₁N₂O₃SNa•0.3H₂O
Calcd.: C, 49.41; H, 4.01; N, 9.60
15 Found : C, 49.55; H, 4.14; N, 9.35
While 500 ml of acetic acid was heated at 120-130°C and stirred, 106.64 g (372.5 mM) of the above ethyl 2-(imidazo[1,2-a]pyridin-5-ylthio)-3-oxo-2-sodiopropionate was added portionwise and the mixture was 20 stirred at 100°C overnight. The solvent was then distilled off under reduced pressure and the residue was diluted with water, neutralized with potassium carbonate with caution, and extracted with 4 portions of chloroform. The organic layers were pooled and 25 dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate = 1/1 to ethyl acetate) and the solid product was rinsed with diethyl ether to provide the title compound.
30 Deep-purple solid. Yield 50.33 g (55%).
3) Synthesis of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid
To a solution of 64.047 g (260.0 mM) of ethyl 5-thia-1,8b-diazaacenaphthylene-4-carboxylate in 400 ml 35 of ethanol was added 156 ml (312 mM) of 2N-aqueous

solution of sodium hydroxide and the mixture was stirred at room temperature for one hour. To this reaction mixture was added concentrated hydrochloric acid with stirring to bring pH into the range of 4-5
5 and the resulting precipitate was recovered by filtration and rinsed serially with ethanol and diethyl ether to provide the title compound.

Red solid. Yield 61.16 g (100%)
¹H-NMR (DMSO-d₆, 200 MHz) δ: 5.97 (1H, dd, 6.6 Hz, 1.2
10 Hz), 6.57-6.73 (2H, m), 6.88 (1H, s), 7.12 (1H, s).

IR (KBr): 3413, 1632, 1338 cm⁻¹.

4) Synthesis of (piperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride
15 While 26.48 g (121.3 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 15.4 g (133 mM) of N-hydroxysuccinimide were stirred together in 250 ml of acetonitrile, 25.6 g (133 mM) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added and
20 the mixture was stirred at room temperature for 6 hours. To this reaction mixture was added 20.3 ml (146 mM) of triethylamine as well as 27.3 g (127 mM) of 1-(tert-butoxycarbonyl)piperidin-4-ylmethylamine and the mixture was stirred at room temperature overnight.
25 This reaction mixture was poured in aqueous solution of sodium hydrogen carbonate and extracted with 3 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄, and the solvent was distilled off under reduced pressure. The residue was subjected to
30 silica gel column chromatography (ethyl acetate to ethyl acetate-methanol = 9:1) to provide crude N-[1-(tert-butoxycarbonyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide. To this crude N-[1-(tert-butoxycarbonyl)piperidin-4-ylmethyl]-5-thia-1,8b-
35 diazaacenaphthylene-4-carboxamide was added 30 ml of concentrated hydrochloric acid and the mixture was

stirred at room temperature for one hour. To this reaction mixture was added ethanol, followed by stirring, and the resulting precipitate was recovered by filtration and rinsed serially with ethanol and
5 diethyl ether to provide the title compound.

Orange-colored solid. Yield 33.347 g (71%)
¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.19-1.54 (2H, m), 1.58-
10 1.92 (3H, m), 2.66-2.96 (2H, m), 2.96-3.15 (2H,
m), 3.16-3.35 (2H, m), 6.65 (1H, d, 7.4 Hz), 7.01
(1H, d, 9.2 Hz), 7.26 (1H, s), 7.32 (1H, dd, 9.2
Hz, 7.4 Hz), 7.70 (1H, s), 8.70-9.28 (3H, m, NH).
IR (KBr): 3358, 1641, 1535 cm⁻¹.

15 5) Synthesis of (R)-N-[1-(1,4-benzodioxan-2-ylmethyl)-
piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-
4-carboxamide

To a solution of 0.410 g (2.467 mM) of (R)-2-hydroxymethyl-1,4-benzodioxane and 0.52 ml (3.70 mM) of triethylamine in 30 ml of diethyl ether was added 0.21 ml (2.71 mM) of methanesulfonyl chloride dropwise with
20 ice-cooling and the mixture was stirred for 0.5 hour.
This reaction mixture was poured in aqueous solution of sodium hydrogen carbonate and extracted with 2 portions of ethyl acetate. The organic layers were combined and dried over MgSO₄ and the solvent was distilled off
25 under reduced pressure. The residue was passed through a short silica gel column (hexane-ethyl acetate = 3/1 to 2/1) to provide crude (S)-2-methanesulfonyloxymethyl-1,4-benzodioxane.

A solution of the above crude (S)-2-methanesulfonyloxymethyl-1,4-benzodioxane, 1.05 g (2.71 mM) of N-(piperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride, and 1.20 ml (8.64 mM) of triethylamine in 30 ml of ethanol was refluxed for 3 days. The solvent was then
35 distilled off under reduced pressure and the residue was purified by silica gel column chromatography (ethyl

acetate to ethyl acetate-methanol = 4/1 to 3/1) to provide the title compound and triethylamine hydrochloride as a mixture. This mixture was diluted with ethyl acetate and washed serially with aqueous 5 solution of sodium hydrogen carbonate, water, and saturated aqueous solution of NaCl. The organic layer was dried over MgSO₄ and the solvent was distilled off to provide the title compound.

Red foam. Yield 0.452 g (40%)
10 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.222-1.368 (2H, m), 1.493-1.702 (3H, m), 2.011-2.187 (2H, m), 2.543 (1H, dd, 6.4 Hz, 13.0 Hz), 2.663 (1H, dd, 5.4 Hz, 13.2 Hz), 2.885-3.035 (2H, m), 3.182 (2H, t, 6.1 Hz), 3.957 (1H, dd, 7.7 Hz, 11.7 Hz), 4.249-4.317 (2H, m), 15 5.759 (1H, dd, 2.5 Hz, 5.5 Hz), 6.371 (1H, br t, 5.9 Hz), 6.600-6.654 (3H, m), 6.788-6.896 (4H, m), 6.990 (1H, s).
IR (neat): 3313, 2924, 1618, 1549, 1491, 1265, 1153, 731 cm⁻¹.

20 6) Synthesis of (R)-N-[1-(1,4-benzodioxan-2-ylmethyl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

In 1 ml of methanol was dissolved 0.452 g of (R)-N-[1-(1,4-benzodioxan-2-ylmethyl)piperidin-4-ylmethyl]-25 5-thia-1,8b-diazaacenaphthylene-4-carboxamide, followed by addition of an excess of methanolic HCl. The mixture was stirred and concentrated to provide the title compound.

Orange-colored foam. Yield 0.530 g
30 ¹H-NMR (CD₃OD, 200 MHz) δ: 1.641-2.042 (5H, m), 3.114-3.588 (6H, m), 3.687-3.881 (2H, m), 4.037 (1H, dd, 6.6 Hz, 11.8 Hz), 4.346 (1H, dd, 2.3 Hz, 11.5 Hz), 4.828-4.905 (1H, m), 6.636 (1H, d, 7.2 Hz), 6.827-6.904 (3H, m), 6.931-6.992 (1H, m), 7.038 (1H, d, 9.2 Hz), 7.098 (1H, s), 7.401 (1H, dd, 7.6 Hz, 8.8 Hz), 7.563 (1H, s).

IR (nujol): 3228, 2650, 1630, 1493, 1294, 1263, 756 cm⁻¹.

Elemental analysis for C₂₅H₂₈Cl₂N₄O₃S•2.5H₂O

Calcd.: C, 51.72; H, 5.73; N, 9.65

5 Found : C, 51.66; H, 5.97; N, 9.62

Example 2

Synthesis of (S)-N-[1-(1,4-benzodioxan-2-ylmethyl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

10 The procedure of Example 1-5) was generally followed to provide (S)-N-[1-(1,4-benzodioxan-2-ylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red foam.

15 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.245-1.395 (2H, m), 1.468-1.719 (3H, m), 2.018-2.210 (2H, m), 2.561 (1H, dd, 5.8 Hz, 13.4 Hz), 2.679 (1H, dd, 5.7 Hz, 13.3 Hz), 2.901-3.059 (2H, m), 3.211 (2H, t, 6.2 Hz), 3.973 (1H, dd, 7.7 Hz, 11.7 Hz), 4.253-4.350 (2H, m), 5.798 (1H, br t, 6.2 Hz), 5.800 (1H, dd, 1.8 Hz, 6.2 Hz), 6.594-6.719 (3H, m), 6.801-6.909 (4H, m), 7.062 (1H, s).

20 IR (neat): 3311, 2924, 1618, 1549, 1491, 1265, 1153, 735 cm⁻¹.

Using the above compound, the procedure of Example 1-6) was generally followed to provide the title compound as orange-colored foam.

25 ¹H-NMR (CD₃OD, 200 MHz) δ: 1.643-2.040 (5H, m), 3.116-3.238 (4H, m), 3.418-3.594 (2H, m), 3.685-3.879 (2H, m), 4.037 (1H, dd, 6.6 Hz, 11.8 Hz), 4.349 (1H, dd, 2.2 Hz, 11.4 Hz), 4.832-4.907 (1H, m), 6.638 (1H, d, 7.2 Hz), 6.829-6.905 (3H, m), 6.933-6.995 (1H, m), 7.040 (1H, d, 9.2 Hz), 7.105 (1H, s), 7.404 (1H, dd, 7.6 Hz, 9.0 Hz), 7.569 (1H, s).

30 IR (nujol): 3230, 2667, 1630, 1493, 1298, 1263, 756 cm⁻¹.

35 Elemental analysis for C₂₅H₂₈Cl₂N₄O₃S•2.0H₂O

Calcd.: C, 52.54; H, 5.64; N, 9.80

Found : C, 52.53; H, 5.86; N, 9.75

Example 3

Synthesis of N-[1-(1,4-benzodioxan-2-ylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

The procedure of Example 1-5) was generally followed to provide N-[1-(1,4-benzodioxan-2-ylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red foam.

¹H-NMR (CDCl₃, 200 MHz) δ: 1.273-1.396 (2H, m), 1.478-1.713 (3H, m), 2.015-2.204 (2H, m), 2.553 (1H, dd, 5.8 Hz, 13.6 Hz), 2.674 (1H, dd, 5.8 Hz, 13.6 Hz), 2.894-3.066 (2H, m), 3.204 (2H, t, 6.1 Hz), 3.968 (1H, dd, 7.8 Hz, 11.6 Hz), 4.242-4.348 (2H, m), 5.788 (1H, dd, 1.6 Hz, 6.0 Hz), 5.865 (1H, br t, 6.2 Hz), 6.583-6.711 (3H, m), 6.794-6.902 (4H, m), 7.047 (1H, s).

IR (neat): 3313, 2926, 1618, 1549, 1491, 1267, 1153, 731 cm⁻¹.

Using the above compound, the procedure of Example 1-6) was generally followed to provide the title compound as orange-colored foam.

¹H-NMR (CD₃OD, 200 MHz) δ: 1.577-2.042 (5H, m), 3.083-3.246 (4H, m), 3.403-3.530 (2H, m), 3.656-3.845 (2H, m), 4.034 (1H, dd, 6.5 Hz, 11.5 Hz), 4.326 (1H, dd, 2.4 Hz, 11.4 Hz), 4.832-4.907 (1H, m), 6.615 (1H, dd, 0.8 Hz, 7.6 Hz), 6.861-6.896 (3H, m), 6.929-6.973 (1H, m), 7.007 (1H, dd, 0.8 Hz, 9.2 Hz), 7.045 (1H, s), 7.393 (1H, dd, 7.5 Hz, 8.9 Hz), 7.539 (1H, s).

IR (nujol): 3217, 2663, 1629, 1493, 1294, 1261, 756 cm⁻¹.

Elemental analysis for C₂₅H₂₈Cl₂N₄O₃S•3.0H₂O

Calcd.: C, 50.93; H, 5.81; N, 9.50

Found : C, 51.11; H, 5.86; N, 9.55

Example 4

Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-3-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

5 1) **Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-3-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide**
To a solution of 0.406 g (1.860 mM) of 5-thia-
1,8b-diazaacenaphthylene-4-carboxylic acid, 0.62 g
(2.05 mM) of 1-(3-phenylpropan-1-yl)piperidin-3-
10 ylmethylamine dihydrochloride, and 1.04 ml (7.44 mM) of
triethylamine in 10 ml of N,N-dimethylformamide was
added 0.34 ml (2.23 mM) of diethyl cyanophosphate at
room temperature and the mixture was stirred at the
prevailing temperature overnight. This reaction
15 mixture was poured in aqueous solution of sodium
hydrogen carbonate and extracted with 3 portions of
ethyl acetate. The organic layers were pooled and
dried over MgSO₄ and the solvent was distilled off
under reduced pressure. The residue was purified by
20 silica gel column chromatography (ethyl acetate to
ethyl acetate-methanol = 4/1 to 2/1) to provide the
title compound.

Red foam Yield 0.300 g (37%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.072-1.187 (1H, m), 1.497-

25 2.045 (8H, m), 2.188 (1H, t, 9.0 Hz), 2.390 (2H,
t, 7.8 Hz), 2.628 (2H, t, 7.7 Hz), 2.708-2.901
(3H, m), 3.202 (1H, dd, 5.2 Hz, 13.6 Hz), 3.324
(1H, dd, 6.1 Hz, 13.3 Hz), 5.702 (1H, dd, 1.6 Hz,
6.2 Hz), 6.537-6.679 (3H, m), 6.859 (1H, br s),
30 6.975 (1H, s), 7.144-7.325 (5H, m).

IR (neat): 3278, 2931, 1618, 1549, 1481, 1281, 1155,
1053, 773, 733, 700 cm⁻¹.

2) **Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-3-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride**

The procedure of Example 1-6) was generally

followed to provide the title compound as orange-colored foam.

5 ¹H-NMR (CD₃OD, 200 MHz) δ: 1.145-1.350 (1H, m), 1.830-2.214 (6H, m), 2.709 (2H, t, 7.5 Hz), 2.784-2.964
 (2H, m), 3.108-3.372 (4H, m), 3.509-3.559 (2H, m),
 6.627 (1H, d, 7.2 Hz), 7.035 (1H, d, 8.8 Hz),
 7.120-7.325 (6H, m), 7.391 (1H, dd, 7.7 Hz, 9.1
 Hz), 7.556 (1H, s).

10 IR (neat): 3390, 2949, 2679, 1633, 1566, 1537, 1450,
 1296, 1215, 754, 702 cm⁻¹.

Elemental analysis for C₂₅H₃₀Cl₂N₄OS•2.5H₂O

Calcd.: C, 54.54; H, 6.41; N, 10.18

Found : C, 54.52; H, 6.40; N, 9.96

Example 5

Synthesis of 4-[1'-(3-phenylpropan-1-yl)-4,4'-bipiperidin-1-ylcarbonyl]-5-thia-1,8b-diazaacenaphthylene dihydrochloride

5 The procedure of Example 4-1) was generally followed to provide 4-[1'-(3-phenylpropan-1-yl)-4,4'-bipiperidin-1-ylcarbonyl]-5-thia-1,8b-diazaacenaphthylene as red foam.

10 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.049-1.382 (6H, m), 1.644-1.903 (8H, m), 2.346 (2H, t, 7.6 Hz), 2.619 (2H, t, 7.7 Hz), 2.817 (2H, br t, 12.3 Hz), 2.964 (2H, br d, 11.2 Hz), 4.354 (2H, br d, 13.4 Hz), 5.705 (1H, dd, 1.5 Hz, 6.3 Hz), 6.045 (1H, s), 6.587 (1H, dd, 9.2 Hz, 16.8 Hz), 6.607 (1H, dd, 9.2 Hz, 12.0 Hz), 6.921 (1H, s), 7.127-7.312 (5H, m).

15 IR (neat): 2937, 1618, 1483, 1439, 1279, 1149, 731 cm⁻¹.

20 Using the above compound, the procedure of Example 1-6) was generally followed to provide the title compound as orange-colored foam.

25 ¹H-NMR (CD₃OD, 200 MHz) δ: 1.145-2.194 (12H, m), 2.707 (2H, t, 7.7 Hz), 2.903-3.154 (6H, m), 3.587 (2H, br d, 11.8 Hz), 4.342 (2H, br d, 12.8 Hz), 6.521 (1H, s), 7.666 (1H, d, 7.4 Hz), 7.096 (1H, d, 8.8 Hz), 7.140-7.330 (5H, m), 7.424 (2H, dd, 7.6 Hz, 9.2 Hz), 7.499 (1H, s).

IR (neat): 2947, 2721, 1630, 1500, 1448, 1390, 1275, 1215, 972, 754, 702 cm⁻¹.

30 Elemental analysis for C₂₉H₃₆Cl₂N₄OS·2.5H₂O
Calcd.: C, 57.61; H, 6.83; N, 9.27
Found : C, 57.56; H, 7.10; N, 8.88

Example 6

Synthesis of N-[2-[1-(3-phenylpropan-1-yl)piperidin-4-ylidene]ethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

35 1) Synthesis of N-[2-(piperidin-4-ylidene)ethyl]-5-

thia-1,8b-diazaacenaphthylene-4-carboxamide
dihydrochloride

To a solution of 2.555 g (7.169 mM) of N-[2-(1-(tert-butoxycarbonyl)piperidin-4-ylidene)ethyl]phthalimide in 30 ml of ethanol was added 0.38 ml (7.89 mM) of hydrazine monohydrate and the mixture was refluxed for one hour. After cooling to room temperature, this reaction mixture was poured in aqueous solution of sodium hydroxide and extracted with 3 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The resulting crude 2-[1-(tert-butoxycarbonyl)piperidin-4-ylidene]ethylamine was not purified but used as it was in the next reaction.

While 1.56 g (7.17 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 0.83 g (7.17 mM) of N-hydroxysuccinimide were stirred together in 50 ml of acetonitrile, 1.51 g (7.89 mM) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added and the mixture was stirred at room temperature for 2 hours. To this reaction mixture was added 1.50 ml (10.8 mM) of triethylamine as well as a solution of the above crude 2-[1-(tert-butoxycarbonyl)piperidin-4-ylidene]ethylamine in 20 ml of acetonitrile and the mixture was stirred at room temperature for 2 hours. This reaction mixture was poured in aqueous solution of sodium hydrogen carbonate and extracted with 3 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was subjected to silica gel column chromatography (ethyl acetate to ethyl acetate-methanol = 9/1) to provide crude N-[2-(1-(tert-butoxycarbonyl)piperidin-4-ylidene)ethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide. To this crude N-[2-(1-(tert-butoxycarbonyl)piperidin-4-

ylidene]ethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide was added 4 ml of concentrated hydrochloric acid and the mixture was stirred at room temperature for 0.5 hour. After addition of ethanol, the mixture 5 was stirred and the resulting precipitate was recovered and rinsed serially with ethanol and diethyl ether to provide the title compound.

Orange-colored solid. Yield 1.117 g (39%)

¹H-NMR (CD₃OD, 200 MHz) δ: 2.460 (2H, t, 5.8 Hz), 2.614
10 (2H, t, 5.8 Hz), 3.169-3.248 (4H, m), 3.856-3.909
(2H, m), 5.427 (1H, t, 7.2 Hz), 6.607 (1H, d, 7.2 Hz), 6.927 (1H, s), 6.987 (1H, d, 9.2 Hz), 7.384 (1H, dd, 7.8 Hz, 9.2 Hz), 7.503 (1H, s).
IR (Nujol): 3498, 3446, 3251, 3190, 3064, 2792, 2476,
15 1626, 1564, 1500, 1281, 1213, 775 cm⁻¹.

2) Synthesis of N-[2-{1-(3-phenylpropan-1-yl)piperidin-4-ylidene]ethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

A solution of 0.508 g (1.272 mM) of N-[2-(piperidin-4-ylidene)ethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride, 0.38 g (1.91 mM) of 1-bromo-3-phenylpropane, and 0.62 ml (4.45 mM) of triethylamine in 20 ml of ethanol was refluxed overnight. The solvent was then distilled off 20 under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate to ethyl acetate-methanol = 4/1) to provide the objective compound and triethylamine hydrochloride as a mixture. This mixture was diluted with ethyl acetate and washed 25 serially with aqueous solution of sodium hydrogen carbonate, water, and saturated aqueous solution of sodium chloride. The organic layer was dried over MgSO₄ and the solvent was distilled off under reduced pressure to provide the title compound.

30 Red liquid. Yield 0.395 g (70%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.749-1.901 (2H, m), 2.196-

2.467 (10H, m), 2.630 (2H, t, 7.7 Hz), 3.870 (2H, t, 6.2 Hz), 5.178 (1H, t, 7.2 Hz), 5.737 (1H, dd, 2.2 Hz, 5.8 Hz), 6.171 (1H, t, 5.2 Hz), 6.534-6.698 (3H, m), 6.968 (1H, s), 7.133-7.308 (5H, m).

5 IR (neat): 3300, 2941, 1616, 1543, 1510, 1481, 1279, 1155, 773, 731, 700 cm⁻¹.

3) Synthesis of N-[2-{1-(3-phenylpropan-1-yl)piperidin-4-ylidene}ethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

10 The procedure of Example 1-6) was generally followed to provide the title compound as orange-colored solid.

15 ¹H-NMR (CD₃OD, 200 MHz) δ: 2.026-2.183 (2H, m), 2.310-2.590 (3H, m), 2.724 (2H, t, 7.5 Hz), 2.936-3.019 (3H, m), 3.097-3.182 (2H, m), 3.539-3.645 (2H, m), 3.805 (1H, dd, 7.0 Hz, 15.4 Hz), 3.922 (1H, dd, 7.8 Hz, 15.2 Hz), 5.431 (1H, t, 7.3 Hz), 6.605 (1H, d, 7.2 Hz), 6.949 (1H, s), 6.991 (1H, d, 8.8 Hz), 7.160-7.305 (5H, m), 7.386 (1H, dd, 7.5 Hz,

20 8.9 Hz), 7.508 (1H, s).

IR (Nujol): 3331, 3250, 3064, 2705-2460, 1632, 1562, 1529, 1498, 1275, 1215, 775, 727 cm⁻¹.

Elemental analysis for C₂₆H₃₀Cl₂N₄OS·2.0H₂O

Calcd.: C, 56.41; H, 6.19; N, 10.12

25 Found : C, 56.39; H, 6.12; N, 10.10

Example 7

Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-2-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

30 1) Synthesis of N-(piperidin-2-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

While 3.605 g (16.519 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 2.09 g (18.2 mM) of N-hydroxysuccinimide were stirred together in 100 ml of acetonitrile, 3.48 g (18.2 mM) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was

added and the mixture was stirred at room temperature for 2 hours. To this reaction mixture was added 3.45 ml (24.8 mM) of triethylamine as well as 2.83 g (24.8 mM) of 2-aminomethylpiperidine and the mixture was
5 stirred at room temperature for one hour. Then, 5.41 g (24.8 mM) of di-tert-butyl dicarbonate was added and the mixture was stirred at room temperature for another hour. This reaction mixture was poured in aqueous solution of sodium hydrogen carbonate and extracted
10 with 3 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄, and the solvent was distilled off under reduced pressure. The residue was subjected to silica gel column chromatography (ethyl acetate to ethyl acetate-methanol = 9/1) to provide
15 crude N-[1-(tert-butoxycarbonyl)piperidin-2-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide. To this crude N-[1-(tert-butoxycarbonyl)piperidin-2-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide was added
5 ml of concentrated hydrochloric acid and the mixture
20 was stirred at room temperature for 0.5 hour. After addition of ethanol, the mixture was stirred and the resulting precipitate was recovered and rinsed serially with ethanol and diethyl ether to provide the title compound.
25 Orange-colored solid. Yield 3.476 g (54%)
¹H-NMR (CD₃OD, 200 MHz) δ: 1.476-1.909 (6H, m), 2.898-
3.022 (1H, m), 3.290-3.504 (4H, m), 6.615 (1H, d,
7.6 Hz), 6.993 (1H, d, 8.8 Hz), 7.068 (1H, s),
7.390 (1H, dd, 7.6 Hz, 8.8 Hz), 7.547 (1H, s).
30 IR (Nujol): 3300, 3199, 3032, 2713, 1633, 1564, 1539,
1500, 1294, 795 cm⁻¹.
2) Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-2-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
The procedure of Example 6-2) was generally
35 followed to provide the title compound.
Red liquid. Yield 0.164 g (15%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.256-1.909 (7H, m), 2.218-2.819 (7H, m), 2.980-3.042 (1H, m), 3.367 (2H, t, 4.3 Hz), 5.705 (1H, dd, 1.4 Hz, 6.2 Hz), 6.532-6.689 (4H, m), 7.001 (1H, s), 7.149-7.318 (5H, m).

5 IR (neat): 3319, 2935, 1618, 1545, 1483, 1281, 1153, 773, 733, 700 cm⁻¹.

3) Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-2-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

10 The procedure of Example 1-7) was generally followed to provide the title compound as orange-colored foam.

15 ¹H-NMR (CD₃OD, 200 MHz) δ: 1.558-2.261 (8H, m), 2.627-2.862 (2H, m), 3.012-3.747 (7H, m), 6.621 (1H, dd, 0.8 Hz, 7.6 Hz), 7.010 (1H, dd, 0.8 Hz, 9.2 Hz), 7.147-7.301 (6H, m), 7.399 (1H, dd, 7.6 Hz, 9.2 Hz), 7.550 (1H, s).

IR (Nujol): 3392, 3061-2545, 1633, 1566, 1537, 1500, 1450, 1294, 1215, 785, 752, 702 cm⁻¹.

20 Elemental analysis for C₂₅H₃₀Cl₂N₄OS•2.0H₂O

Calcd.: C, 55.45; H, 6.33; N, 10.35

Found : C, 55.61; H, 6.35; N, 10.14

Example 8

25 Synthesis of N-[2-[1-(3-phenylpropan-1-yl)-1,2,3,6-tetrahydropyridin-4-yl]ethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

30 The procedure of Example 6-1) was generally followed to provide N-[2-(1,2,3,6-tetrahydropyridin-4-yl)ethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored solid.

35 ¹H-NMR (CD₃OD, 200 MHz) δ: 2.271-2.392 (4H, m), 3.193-3.429 (4H, m), 3.639 (2H, br s), 5.529 (1H, br s), 6.606 (1H, d, 7.8 Hz), 6.988 (1H, d, 8.6 Hz), 6.991 (1H, s), 7.383 (1H, dd, 8.0 Hz, 8.8 Hz), 7.513 (1H, s).

IR (Nujol): 3516, 3454, 3244, 3061, 2791-2339, 1633,

1566, 1533, 1498, 1304, 1263, 1213, 829, 773, 735
cm⁻¹.

Using the above compound, the procedure of Example
6-2) was generally followed to provide N-[2-[1-(3-
5 phenylpropan-1-yl)-1,2,3,6-tetrahydropyridin-4-
yl]ethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
as red foam.

10 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.797-1.951 (2H, m), 2.143-
2.227 (4H, m), 2.467 (2H, t, 7.7 Hz), 2.573 (2H,
d, 5.4 Hz), 2.650 (2H, t, 7.5 Hz), 2.986 (2H, br
s), 3.385 (2H, q, 6.4 Hz), 5.455 (1H, s), 5.720
(1H, dd, 1.8 Hz, 6.2 Hz), 6.259 (1H, t, 5.5 Hz),
6.524-6.609 (2H, m), 6.651 (1H, s), 6.975 (1H, s),
7.133-7.323 (5H, m).

15 IR (neat): 3277, 2939, 1618, 1549, 1481, 1281, 1155,
773, 731, 700 cm⁻¹.

Using the above compound, the procedure of Example
1-6) was generally followed to provide the title
compound as orange-colored foam.

20 ¹H-NMR (CD₃OD, 200 MHz) δ: 2.061-2.220 (3H, m), 2.269-
2.379 (2H, m), 2.606 (1H, br s), 2.738 (2H, t, 7.7
Hz), 3.176-3.350 (4H, m), 3.407-3.661 (3H, m),
3.880 (1H, br d, 15.4 Hz), 5.493 (1H, br s), 6.606
(1H, d, 7.6 Hz), 7.027 (1H, d, 9.2 Hz), 7.145-
25 7.294 (6H, m), 7.381 (1H, dd, 7.7 Hz, 8.7 Hz),
7.537 (1H, s).

IR (neat): 3390, 3060-2602, 1633, 1566, 1535, 1500,
1446, 1296, 1215, 785, 754, 702 cm⁻¹.

Elemental analysis for C₂₆H₃₀Cl₂N₄OS·2.5H₂O
30 Calcd.: C, 55.51; H, 6.27; N, 9.96
Found : C, 55.37; H, 6.42; N, 9.94

Example 9

Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-
ylmethyl]-3-(5-thia-1,8b-diazaacenaphthylen-4-yl)acryl-
35 amide dihydrochloride

1) Synthesis of 5-thia-1,8b-diazaacenaphthylene-4-

methanol

To 10.757 g (43.676 mM) of ethyl 5-thia-1,8b-diazaacenaphthylene-4-carboxylate in 200 ml of dichloromethane was added a 20 ml (approx.) portion of 5 87.4 ml (131 mM) of 1.5M diisobutylaluminum hydride-toluene at -78°C and the temperature was increased to about 0°C. After this mixture was cooled to -78°C again, about 30 ml of 1.5M diisobutylaluminum hydride-toluene was added and the temperature was increased to 10 about 0°C. This reaction mixture was further cooled to -78°C and the remainder of 1.5M diisobutylaluminum hydride-toluene was added. The mixture was stirred at the prevailing temperature for 0.5 hour. To this reaction mixture was added methanol at -78°C to 15 decompose the excess diisobutylaluminum hydride. Then, water was added with caution under ice-cooling until a precipitate had formed. The precipitate was filtered off with the aid of celite and washed with aqueous dimethyl sulfoxide. From the pooled filtrate, the 20 solvent was distilled off under reduced pressure and the solid residue was rinsed with diethyl ether to provide the title compound.

Yellow solid. Yield 7.777 g (87%)

25 $^1\text{H-NMR}$ (DMSO-d₆, 200 MHz) δ: 3.804 (2H, s), 5.330 (1H, br s), 5.945 (1H, dd, 2.2 Hz, 5.6 Hz), 6.123 (1H, s), 6.596-6.706 (2H, m), 6.883 (1H, s).
IR (Nujol): 3429, 3084, 1481, 1090, 1028, 851, 767, 727 cm⁻¹.

30 2) Synthesis of 3-(5-thia-1,8b-diazaacenaphthylen-4-yl)acrylic acid

To a solution of 7.777 g (38.076 mM) of 5-thia-1,8b-diazaacenaphthylene-4-methanol in ethyl acetate (50 ml)-N,N-dimethylformamide (50 ml) was added 23 g of active manganese dioxide and the mixture was stirred at 35 room temperature for 4 hours. The reaction mixture was filtered and the precipitate was washed with N,N-

dimethylformamide. The pooled filtrate was distilled under reduced pressure to remove the solvent. The crude 5-thia-1,8b-diazaacenaphthylene-4-carbaldehyde thus obtained was not purified but used as it was in the next reaction. To a solution of 9.39 g (41.9 mM) of ethyl diethylphosphonoacetate in 50 ml of toluene was added 1.68 g (41.9 mM) of a 60% suspension of sodium hydride in liquid paraffin at room temperature and the mixture was stirred for 0.5 hour. This mixture was added to a solution of the above crude 5-thia-1,8b-diazaacenaphthylene-4-carbaldehyde in N,N-dimethylformamide (50 ml)-toluene (200 ml) under ice cooling and the mixture was stirred at room temperature for one hour. This reaction mixture was poured in water and extracted with 3 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The resulting crude ethyl 3-(5-thia-1,8b-diazaacenaphthylen-4-yl)acrylate was not purified but used as it was in the next reaction. To a solution of the above crude ethyl 3-(5-thia-1,8b-diazaacenaphthylen-4-yl)acrylate in 300 ml of ethanol was added 60 ml (120 mM) of 2N-aqueous solution of sodium hydroxide and the mixture was stirred at room temperature for 3 hours. To this reaction mixture was added concentrated hydrochloric acid (ca 10 ml) with stirring to bring the pH into the range of 4-5 and the resulting precipitate was recovered by filtration and rinsed serially with ethanol and diethyl ether to provide the title compound.

Red solid. Yield 7.777 g (84%)

¹H-NMR (DMSO-d₆, 200 MHz) δ: 5.529 (1H, d, 15.8 Hz), 6.262 (1H, dd, 1.4 Hz, 6.6 Hz), 6.795-6.939 (3H, m), 7.226 (1H, d, 16.0 Hz), 7.266 (1H, s).

IR (Nujol): 2521, 1711, 1587, 1309, 1255, 1136, 1107, 947, 970 cm⁻¹.

3) Synthesis of N-(piperidin-4-ylmethyl)-3-(5-thia-1,8b-diazaacenaphthylen-4-yl)acrylamide dihydrochloride
While 0.708 g (2.898 mM) of 3-(5-thia-1,8b-diazaacenaphthylen-4-yl)acrylic acid, 0.68 g (3.19 mM) of 1-(tert-butoxycarbonyl)piperidin-4-ylmethyamine, and 0.48 ml (3.48 mM) of triethylamine were stirred together in 10 ml of N,N-dimethylformamide, 0.53 ml (3.48 mM) of diethyl cyanophosphate was added dropwise at room temperature and the mixture was stirred at the prevailing temperature overnight. This reaction mixture was poured in aqueous solution of sodium hydrogen carbonate and extracted with 3 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was subjected to silica gel column chromatography (ethyl acetate to ethyl acetate-methanol = 9/1) to provide crude N-[1-(tert-butoxycarbonyl)piperidin-4-ylmethyl]-3-(5-thia-1,8b-diazaacenaphthylen-4-yl)acrylamide.

To this crude N-[1-(tert-butoxycarbonyl)piperidin-4-ylmethyl]-3-(5-thia-1,8b-diazaacenaphthylen-4-yl)acrylamide was added 1 ml of concentrated hydrochloric acid and the mixture was stirred at room temperature for 0.5 hour. After addition of ethanol, the mixture was stirred and the resulting precipitate was collected and washed serially with ethanol and diethyl ether to provide the title compound. Orange-colored solid. Yield 1.099 g (92%)
¹H-NMR (CD₃OD, 200 MHz) δ: 1.335-1.635 (2H, m), 1.794-2.072 (3H, m), 2.907-3.035 (2H, m), 3.227-3.438 (4H, m), 6.173 (1H, d, 15.4 Hz), 6.743 (1H, s), 6.751 (1H, d, 7.4 Hz), 7.141 (1H, d, 8.8 Hz), 7.195 (1H, d, 15.4 Hz), 7.504 (1H, dd, 7.8 Hz, 9.2 Hz), 7.546 (1H, s).

IR (Nujol): 3373, 2735, 1666, 1637, 1606, 1552, 1381, 1344, 1302, 1261, 1215, 962, 777 cm⁻¹.

4) Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-ylmethyl]-3-(5-thia-1,8b-diazaacenaphthylen-4-yl)acrylamide

A solution of 0.502 g (1.214 mM) of N-(piperidin-4-ylmethyl)-3-(5-thia-1,8b-diazaacenaphthylen-4-yl)acrylamide dihydrochloride, 0.36 g (1.82 mM) of 1-bromo-3-phenylpropane, and 0.59 ml (4.25 mM) of triethylamine in 20 ml of ethanol was refluxed for one day. The solvent was then distilled off under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate to ethyl acetate-methanol = 4/1), whereby a mixture of the objective compound and triethylamine hydrochloride was obtained. This mixture was diluted with ethyl acetate and washed serially with aqueous solution of sodium hydrogen carbonate, water, and saturated aqueous solution of sodium chloride. The organic layer was dried over MgSO₄ and the solvent was distilled off under reduced pressure to provide the title compound.

20 Red foam. Yield 0.305 g (55%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.229-1.401 (2H, m), 1.482-1.958 (7H, m), 2.354 (2H, t, 7.7 Hz), 2.612 (2H, t, 7.7 Hz), 2.896-2.954 (2H, m), 3.231 (2H, t, 6.0 Hz), 5.659 (1H, d, 15.2 Hz), 5.859 (1H, dd, 1.2 Hz, 6.6 Hz), 6.222 (1H, br t, 5.8 Hz), 6.255 (1H, s), 6.598-6.746 (2H, m), 7.048-7.305 (7H, m).
25 IR (neat): 3273, 2926, 1651, 1614, 1585, 1554, 1344, 1265, 1213, 1142, 964, 773, 731, 700 cm⁻¹.

5) Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-ylmethyl]-3-(5-thia-1,8b-diazaacenaphthylen-4-yl)acrylamide dihydrochloride

In 2 ml of methanol was dissolved 0.305 g of N-[1-(3-phenylpropan-1-yl)piperidin-4-ylmethyl]-3-(5-thia-1,8b-diazaacenaphthylen-4-yl)acrylamide, followed by 35 addition of a stoichiometric excess of methanolic hydrochloric acid. The mixture was stirred and

concentrated and the residue was crystallized from ethanol-diethyl ether to provide the title compound.

Orange-colored solid. Yield 0.342 g

¹H-NMR (CD₃OD, 200 MHz) δ: 1.405-2.610 (2H, m), 1.790-

5 2.140 (5H, m), 2.711 (2H, t, 7.5 Hz), 2.868-3.244 (6H, m), 3.553-3.616 (2H, m), 6.149 (1H, d, 15.4 Hz), 6.735 (1H, s), 6.792 (1H, d, 7.2 Hz), 7.109-7.334 (7H, m), 7.496 (1H, dd, 7.8 Hz, 9.2 Hz), 7.537 (1H, s).

10 IR (Nujol): 3255, 2669, 1637, 1601, 1545, 1301, 1263, 1215, 1159, 970, 777, 752, 727, 700 cm⁻¹.

Elemental analysis for C₂₇H₃₂C₁₂N₄OS•2.0H₂O

Calcd.: C, 57.14; H, 6.39; N, 9.87

Found : C, 57.44; H, 6.27; N, 9.80

15 Example 10

Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-3-(5-thia-1,8b-diazaacenaphthylen-4-yl)acrylamide dihydrochloride

The procedure of Example 9-3) was generally followed to provide N-(piperidin-4-yl)-3-(5-thia-1,8b-diazaacenaphthylen-4-yl)acrylamide dihydrochloride as orange-colored solid.

17 ¹H-NMR (CD₃OD, 200 MHz) δ: 1.641-1.844 (2H, m), 2.123-2.174 (2H, m), 3.072-3.466 (4H, m), 3.978-4.132 (1H, m), 6.138 (1H, d, 15.4 Hz), 6.741 (1H, s), 6.789 (1H, d, 7.4 Hz), 7.128 (1H, d, 8.4 Hz), 7.211 (1H, d, 15.8 Hz), 7.494 (1H, dd, 7.8 Hz, 9.2 Hz), 7.536 (1H, s).

IR (Nujol): 3485, 3413, 3230, 2725, 1664, 1639, 1605, 30 1549, 1302, 1263, 1213, 993, 781 cm⁻¹.

Using the above compound, the procedure of Example 6-2) was generally followed to provide N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-3-(5-thia-1,8b-diazaacenaphthylen-4-yl)acrylamide as red foam.

35 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.423-1.597 (2H, m), 1.731-2.147 (6H, m), 2.366 (2H, t, 7.7 Hz), 2.616 (2H,

t, 7.7 Hz), 2.834-2.892 (2H, m), 3.799-3.944 (1H, m), 5.665 (1H, d, 15.0 Hz), 5.845 (1H, d, 6.6 Hz), 6.171 (1H, d, 8.0 Hz), 6.253 (1H, s), 6.590-6.737 (2H, m), 7.043 (1H, s), 7.118-7.307 (6H, m).

5 IR (neat): 3265, 2943, 1649, 1614, 1585, 1551, 1348, 1267, 1213, 1142, 1113, 960, 910, 773, 731, 700 cm⁻¹.

Using the above compound, the procedure of Example 1-6) was generally followed to provide the title 10 compound as orange-colored solid.

¹H-NMR (CD₃OD, 200 MHz) δ: 1.711-1.908 (2H, m), 2.048-2.218 (4H, m), 2.720 (2H, t, 7.5 Hz), 3.011-3.222 (4H, m), 3.590-3.654 (2H, m), 3.929-4.205 (1H, m), 6.113 (0.8H, d, 15.4 Hz), 6.321 (0.2H, d, 16.0 Hz), 6.737 (1H, s), 6.790 (1H, d, 7.2 Hz), 7.109-7.339 (7H, m), 7.495 (1H, dd, 7.6 Hz, 9.2 Hz), 7.539 (1H, s).

15 IR (Nujol): 3369, 3184, 1486, 1655, 1637, 1597, 1552, 1215, 1159, 980, 837, 783, 758, 727 cm⁻¹.

20 Elemental analysis for C₂₆H₃₀Cl₂N₄OS•1.4H₂O

Calcd.: C, 57.54; H, 6.09; N, 10.32

Found : C, 57.74; H, 6.07; N, 10.17

Example 11

Synthesis of N-[2-(3-phenylpropan-1-yl)-2,3-dihydro-1H-25 isoindol-5-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[2-(3-phenylpropan-1-yl)-2,3-dihydro-1H-isoindol-5-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

30 To a solution of 0.401 g (1.011 mM) of N-[2-(3-phenylpropan-1-yl)-2,3-dihydro-1H-isoindol-5-ylmethyl]-phthalimide in 20 ml of ethanol was added 0.05 ml (1.11 mM) of hydrazine monohydrate and the mixture was refluxed for 2 hours. After cooling to room 35 temperature, the precipitate that had formed was filtered off and washed with ethanol. From the pooled

filtrate, the solvent was distilled off. The resulting crude N-[2-(3-phenylpropan-1-yl)-2,3-dihydro-1H-isoindol-5-yl]methylamine was not purified but used as it was in the next reaction. To a solution of 0.22 g (1.21 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid, the above crude N-[2-(3-phenylpropan-1-yl)-2,3-dihydro-1H-isoindol-5-yl]methylamine, and 0.17 ml (1.21 mM) of triethylamine in 20 ml of N,N-dimethylformamide was added 0.18 ml (1.21 mM) of diethyl cyanophosphate dropwise at room temperature with constant stirring and the mixture was stirred at the prevailing temperature for 3 days. This reaction mixture was poured in aqueous solution of sodium hydrogen carbonate and extracted with 3 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate to ethyl acetate-methanol = 9/1) to provide the title compound.

Red liquid. Yield 0.109 g (23%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.870-1.985 (2H, m), 2.714 (2H, t, 8.0 Hz), 2.751 (2H, t, 7.3 Hz), 3.913 (4H, s), 4.399 (2H, d, 5.8 Hz), 5.715 (1H, dd, 2.9 Hz, 4.9 Hz), 6.571 (1H, dd, 9.2 Hz, 11.2 Hz), 6.591 (1H, s), 6.664 (1H, s), 6.672 (1H, br t, 5.3 Hz), 6.907 (1H, s), 7.058-7.332 (8H, m).
IR (neat): 3275, 2935, 1618, 1545, 1481, 1281, 1153, 1032, 771, 731, 700 cm⁻¹.
2) Synthesis of N-[2-(3-phenylpropan-1-yl)-2,3-dihydro-1H-isoindol-5-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride
The procedure of Example 1-6) was generally followed to provide the title compound as brown solid.
¹H-NMR (CD₃OD, 200 MHz) δ: 1.070-2.227 (2H, m), 2.764 (2H, t, 7.7 Hz), 3.401-3.482 (2H, m), 4.427 (2H,

s), 4.482-4.553 (2H, m), 4.836-4.878 (2H, m),
6.587 (1H, d, 7.4 Hz), 6.991 (1H, d, 8.8 Hz),
6.995 (1H, s), 7.149-7.415 (9H, m), 7.512 (1H, s).

IR (neat): 3251, 3131, 2924, 2515, 1633, 125, 1498,
5 1443, 1296, 1219 cm⁻¹.

Elemental analysis for C₂₈H₂₈Cl₂N₄OS·4.5H₂O

Calcd.: C, 54.19; H, 6.01; N, 9.03

Found : C, 53.99; H, 5.63; N, 9.38

Example 12

10 Synthesis of N-[2-[1-(3-phenylpropan-1-yl)-2,5-dihydro-
1H-pyrrol-3-yl]ethyl]-5-thia-1,8b-diazaacenaphthylene-
4-carboxamide dihydrochloride

The procedure of Example 6-1) was generally
followed to provide N-[2-(2,5-dihydro-1H-pyrrol-3-
15 yl)ethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
dihydrochloride as orange-colored solid.

1H-NMR (CD₃OD, 200 MHz) δ: 2.445 (2H, t, 6.4 Hz), 3.440
(2H, t, 6.8 Hz), 4.048 (4H, s), 5.645 (1H, s),
6.614 (1H, d, 7.8 Hz), 6.996 (1H, d, 8.4 Hz),
20 7.006 (1H, s), 7.389 (1H, dd, 7.6 Hz, 9.2 Hz),
7.528 (1H, s).

IR (Nujol): 3358, 3226, 2665, 1657, 1633, 1564, 1535,
1498, 1282, 1209, 777 cm⁻¹.

Using the above compound, the procedure of Example
25 6-2) was generally followed to provide N-[2-[1-(3-
phenylpropan-1-yl)-2,5-dihydro-1H-pyrrol-3-yl]ethyl]-5-
thia-1,8b-diazaacenaphthylene-4-carboxamide as red
liquid.

1H-NMR (CDCl₃, 200 MHz) δ: 1.742-1.894 (2H, m), 2.291
30 (2H, t, 6.2 Hz), 2.645 (2H, t, 7.5 Hz), 2.667 (2H,
t, 7.7 Hz), 3.367-3.460 (6H, m), 5.489 (1H, s),
5.721 (1H, dd, 2.2 Hz, 5.4 Hz), 6.524 (1H, t, 5.1
Hz), 6.570-6.627 (3H, m), 6.960 (1H, s), 7.134-
7.327 (5H, m).

35 IR (neat): 3242, 2937, 1618, 1549, 1510, 1481, 1281,
1153, 910, 773, 731, 700 cm⁻¹.

Using the above compound, the procedure of Example 1-6) was generally followed to provide the title compound as orange-colored foam.

¹H-NMR (CD₃OD, 200 MHz) δ: 1.991-2.149 (2H, m), 2.421

5 (2H, t, 6.2 Hz), 2.747 (2H, t, 7.7 Hz), 3.290-3.513 (4H, m), 3.914-4.052 (2H, m), 4.240-4.334 (2H, m), 5.634 (1H, s), 6.598 (1H, d, 7.4 Hz), 6.993 (1H, d, 9.0 Hz), 7.043 (1H, s), 7.144-7.299 (5H, m), 7.385 (1H, dd, 7.4 Hz, 9.2 Hz), 7.517 (1H, s).

IR (neat): 3062, 2945, 2675, 2486, 1633, 1566, 1537, 1500, 1448, 1296, 1215, 785, 756, 702 cm⁻¹.

Elemental analysis for C₂₃H₂₈Cl₂N₄OS·2.0H₂O

Calcd.: C, 55.66; H, 5.98; N, 10.38

15 Found : C, 55.88; H, 6.33; N, 10.32

Example 13

Synthesis of N-[4-[4-(2-chlorobenzylidene)piperidino]-butyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

20 The procedure of Example 11-1) was generally followed to provide N-[4-[4-(2-chlorobenzylidene)-piperidino]butyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red liquid.

¹H-NMR (CDCl₃, 200 MHz) δ: 1.565-1.628 (4H, m), 2.377-2.500 (8H, m), 2.598 (2H, t, 5.2 Hz), 3.282-3.339 (2H, m), 5.759 (1H, dd, 2.0 Hz, 6.0 Hz), 6.307 (1H, s), 6.551-6.689 (4H, m), 7.007 (1H, s), 7.116-7.247 (3H, m), 7.352-7.408 (1H, m).

IR (neat): 3304, 2941, 1618, 1549, 1510, 1479, 1281, 30 1155, 910, 773, 731 cm⁻¹.

Using the above compound, the procedure of Example 1-6) was generally followed to provide the title compound as orange-colored solid.

¹H-NMR (CD₃OD, 200 MHz) δ: 1.577-1.705 (2H, m), 1.764-1.916 (2H, m), 2.469-3.103 (6H, m), 3.193 (2H, br t, 8.1 Hz), 3.317 (2H, t, 6.6 Hz), 3.552-3.762

(2H, m), 6.556 (1H, s), 6.609 (1H, d, 7.4 Hz),
6.997 (1H, d, 8.8 Hz), 7.037 (1H, s), 7.239-7.448
(5H, m), 7.526 (1H, s).

IR (Nujol): 3213, 2721, 1632, 1498, 1292, 1215, 750,
5 725 cm⁻¹.

Elemental analysis for C₂₆H₂₉Cl₃N₄OS·3.5H₂O

Calcd.: C, 50.78; H, 5.90; N, 9.11

Found : C, 51.04; H, 5.74; N, 9.30

Example 14

10 Synthesis of N-[4-(4-hydroxy-4-phenylpiperidino)butyl]-
5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydro-
chloride

15 The procedure of Example 11-1) was generally
followed to provide N-[4-(4-hydroxy-4-
phenylpiperidino)butyl]-5-thia-1,8b-
diazaacenaphthylene-4-carboxamide as red foam.

1H-NMR (CDCl₃, 200 MHz) δ: 1.584-1.826 (7H, m), 2.186
(2H, dt, 4.1 Hz, 13.1 Hz), 2.392-2.546 (4H, m),
2.812-2.867 (2H, m), 3.260-3.337 (2H, m), 5.716
20 (1H, dd, 1.8 Hz, 5.8 Hz), 6.539-6.656 (4H, m),
6.942 (1H, s), 7.213-7.402 (3H, m), 7.501-7.548
(2H, m).

IR (neat): 3305, 2943, 1618, 1547, 1510, 1481, 1282,
1153, 910, 770, 731, 700 cm⁻¹.

25 Using the above compound, the procedure of Example
1-6) was generally followed to provide the title
compound as orange-colored solid.

1H-NMR (CD₃OD, 200 MHz) δ: 1.593-2.012 (6H, m), 2.425
(2H, dt, 4.8 Hz, 13.7 Hz), 3.218 (2H, t, 8.2 Hz),
30 3.292-3.576 (6H, m), 6.616 (1H, d, 7.6 Hz), 6.999
(1H, d, 10.4 Hz), 7.025 (1H, s), 7.231-7.436 (4H,
m), 7.507-7.584 (3H, m).

IR (Nujol): 3211, 2673, 1630, 1497, 1292, 1213, 976,
766, 725, 700 cm⁻¹.

35 Elemental analysis for C₂₅H₃₀Cl₂N₄O₂S·1.5H₂O

Calcd.: C, 54.74; H, 6.06; N, 10.21

Found : C, 54.42; H, 6.44; N, 10.10

Example 15

Synthesis of N-[2-hydroxy-3-(4-phenylpiperidino)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

The procedure of Example 11-1) was generally followed to provide N-[2-hydroxy-3-(4-phenylpiperidino)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red foam.

10 $^1\text{H-NMR}$ (CDCl_3 , 200 MHz) δ : 1.623-1.890 (4H, m), 2.126 (1H, dt, 2.4 Hz, 11.5 Hz), 2.293-2.620 (5H, m), 2.919-3.131 (2H, m), 3.236 (1H, td, 6.0 Hz, 13.7 Hz), 3.558 (1H, ddd, 3.7 Hz, 5.6 Hz, 13.7 Hz), 3.813-3.932 (1H, m), 5.759 (1H, dd, 1.6 Hz, 6.2 Hz), 6.525 (1H, br t, 5.0 Hz), 6.561-6.684 (3H, m), 7.031 (1H, s), 7.172-7.352 (5H, m).

IR (neat): 3311, 2933, 2808, 1618, 1543, 1506, 1483, 1281, 1155, 910, 773, 731, 700 cm^{-1} .

Using the above compound, the procedure of Example 20 1-6) was generally followed to provide the title compound as orange-colored solid.

15 $^1\text{H-NMR}$ (CD_3OD , 200 MHz) δ : 2.092 (4H, br s), 2.820-2.970 (1H, m), 3.147-3.425 (6H, m), 3.724-3.786 (2H, m), 4.190-4.300 (1H, m), 6.619 (1H, d, 7. Hz), 7.000 (1H, d, 9.2 Hz), 7.078 (1H, s), 7.221-7.437 (6H, m), 7.550 (1H, s).

20 IR (Nujol): 3242, 2723, 1633, 1498, 1296, 1215, 1113, 783, 702 cm^{-1} .

Elemental analysis for $\text{C}_{24}\text{H}_{28}\text{Cl}_2\text{N}_4\text{O}_2\text{S} \cdot 2.0\text{H}_2\text{O}$

30 Calcd.: C, 53.04; H, 5.93; N, 10.31
Found : C, 53.09; H, 6.11; N, 10.31

Example 16

Synthesis of N-[2-oxo-3-(4-phenylpiperidino)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

35 1) Synthesis of N-[2-oxo-3-(4-phenylpiperidino)propan-

1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a solution of 0.39 g (3.05 mM) of oxalyl chloride in 20 ml of dichloromethane was added 0.43 ml (6.11 mM) of dimethyl sulfoxide dropwise at -78°C. The mixture was stirred for 5 minutes, at the end of which time a solution of 0.885 g (2.037 mM) of N-[2-hydroxy-3-(4-phenylpiperidino)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in 20 ml of dichloromethane was added and the mixture was stirred at -78°C for 15 minutes. To this mixture was added 1.70 ml (12.2 mM) of triethylamine and the temperature was increased to room temperature. This reaction mixture was poured in water and extracted with 3 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The resulting crude product was purified by silica gel column chromatography (ethyl acetate to ethyl acetate-methanol = 9/1 to 4/1) to provide the title compound.

20 Red foam. Yield 0.652 g (74%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.812-1.903 (4H, m), 2.195-2.324 (2H, m), 2.423-2.580 (1H, m), 2.910-2.967 (2H, m), 3.278 (2H, s), 4.354 (2H, d, 4.6 Hz), 5.789 (1H, dd, 1.9 Hz, 6.1 Hz), 6.581-6.722 (4H, m), 7.063 (1H, s), 7.166-7.357 (5H, m).
IR (neat): 3257, 2935, 1731, 1616, 1539, 1504, 1483, 1282, 1153, 910, 773, 731, 700 cm⁻¹.

25 2) Synthesis of N-[2-oxo-3-(4-phenylpiperidino)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

The procedure of Example 1-6) was generally followed to provide the title compound as orange-colored solid.

30 ¹H-NMR (CD₃OD, 200 MHz) δ: 2.050-2.150 (4H, m), 2.841-3.000 (1H, m), 3.180-3.321 (2H, m), 3.629-3.691 (2H, m), 4.215 (2H, s), 4.444 (2H, s), 6.625 (1H,

d, 7.2 Hz), 7.007 (1H, d, 9.2 Hz), 7.039 (1H, s),
7.195-7.442 (6H, m), 7.557 (1H, s).

IR (Nujol): 3234, 2723, 1743, 1633, 1498, 1300, 1215,
968, 779, 725, 700 cm⁻¹.

5 Elemental analysis for C₂₄H₂₆Cl₂N₄O₂S·2.5H₂O

Calcd.: C, 52.36; H, 5.68; N, 10.18

Found : C, 52.65; H, 5.72; N, 10.08

Example 17

10 Synthesis of N-[2-[(4-phenylpiperidino)methyl]benzyl]-
5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydro-
chloride

15 The procedure of Example 11-1) was generally
followed to provide N-[2-[(4-phenylpiperidino)methyl]-
benzyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
as red solid.

19 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.787-2.030 (4H, m), 2.207
(2H, dt, 2.3 Hz, 11.8 Hz), 2.619 (1H, tt, 3.9 Hz,
12.0 Hz), 3.109 (2H, br d, 11.6 Hz), 3.549 (2H,
s), 4.484 (2H, d, 5.0 Hz), 5.418 (1H, dd, 0.8 Hz,
6.8 Hz), 6.460 (1H, dd, 6.8 Hz, 9.2 Hz), 6.535
(1H, s), 6.598 (1H, dd, 0.9 Hz, 9.2 Hz), 6.768
(1H, s), 7.154-7.453 (9H, m), 8.127 (1H, br s).

20 IR (Nujol): 3296, 1647, 1597, 1516, 1485, 1244, 1140,
741 cm⁻¹.

25 Using the above compound, the procedure of Example
1-6) was generally followed to provide the title
compound as orange-colored solid.

29 ¹H-NMR (CD₃OD, 200 MHz) δ: 2.053-2.125 (4H, m), 2.883-
3.044 (1H, m), 3.224-3.367 (2H, m), 3.585-3.667
(2H, m), 4.566 (4H, s), 6.584 (1H, d, 7.6 Hz),
7.017 (1H, d, 8.8 Hz), 7.182-7.631 (12H, m).

30 IR (Nujol): 3392, 2698, 1610, 1572, 1311, 1207, 760
cm⁻¹.

Elemental analysis for C₂₉H₃₀Cl₂N₄OS·1.0H₂O

35 Calcd.: C, 60.94; H, 5.64; N, 9.80

Found : C, 60.67; H, 5.78; N, 9.74

Example 18

Synthesis of N-(1-phenethylpiperidin-4-yl)-3-(5-thia-1,8b-diazaacenaaphthylen-4-yl)acrylamide dihydrochloride

1) **Synthesis of N-(1-phenethylpiperidin-4-yl)-3-(5-thia-1,8b-diazaacenaaphthylen-4-yl)acrylamide**

In 10 ml of ethanol was suspended 0.998 g (2.5 mM) of N-(piperidin-4-yl)-3-(5-thia-1,8b-diazaacenaaphthylen-4-yl)acrylamide dihydrochloride as well as 0.703 g (3.8 mM) of phenethyl bromide, followed by addition of 1.74 ml (12.5 mM) of triethylamine, and the mixture was refluxed for 5 hours. To this reaction mixture was further added 0.070 g (0.38 mM) of phenethyl bromide, and the mixture was refluxed overnight. This reaction mixture was diluted with 5% aqueous solution of sodium hydrogen carbonate and extracted with dichloromethane. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over Na₂SO₄, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate-methanol = 4/1) and concentrated and the residue was crystallized from ether to provide the title compound.

Red solid. Yield 0.544 g (51%)

25 ¹H-NMR (CDCl₃) δ: 1.45-1.80 (4H, m), 1.90-2.10 (2H, m), 2.15-2.35 (2H, m), 2.60-2.75 (2H, m), 2.80-2.90 (2H, m), 2.93-3.10 (2H, m), 3.83-4.05 (1H, m), 5.44-5.48 (1H, m), 5.61 (1H, d, 15.0 Hz), 5.88 (1H, d, 6.2 Hz), 6.29 (1H, s), 6.63-6.78 (2H, m), 30 7.08 (1H, s), 7.15-7.35 (4H, m).

IR (KBr): 3392, 3224, 3035, 2941, 1647, 1614, 1578, 1363, 1263, 1142, 1111, 995, 966, 750, 702 cm⁻¹.

2) **Synthesis of N-(1-phenethylpiperidin-4-yl)-3-(5-thia-1,8b-diazaacenaaphthylen-4-yl)acrylamide dihydrochloride**

35 The procedure of Example 1-7) was generally

followed to provide the title compound as orange-colored solid.

¹H-NMR (CD₃OD) δ: 1.75-2.00 (2H, m), 2.05-2.35 (4H, m),

3.00-3.25 (4H, m), 3.30-3.50 (2H, m), 3.65-3.80

5 (2H, m), 3.90-4.30 (1H, m), 6.12 (0.8H, d, 15.4 Hz), 6.33 (0.2H, d, 15.0 Hz), 6.94 (1H, s), 6.77

(1H, d, 7.4 Hz), 7.10-7.48 (6H, m), 7.53 (1H, s).

IR (KBr): 3425, 3240, 3052, 2947, 2684, 1659, 1605, 1551, 1504, 1394, 1360, 1217, 1151, 966, 764 cm⁻¹.

10 Elemental analysis for C₂₅H₂₈N₄OSCl₂·0.5H₂O

Calcd.: C, 58.59; H, 5.70; N, 10.93

Found : C, 58.65; H, 5.81; N, 11.11

Example 19

15 Synthesis of N-(1-phenethylpiperidin-4-ylmethyl)-3-(5-thia-1,8b-diazaacenaphthylen-4-yl)acrylamide dihydrochloride

20 The procedure of Example 18-1) was generally followed to provide N-(1-phenethylpiperidin-4-ylmethyl)-3-(5-thia-1,8b-diazaacenaphthylen-4-yl)acrylamide as red solid.

¹H-NMR (CDCl₃) δ: 1.25-1.50 (2H, m), 1.50-1.80 (3H, m),

1.95-2.20 (4H, m), 2.56-2.64 (2H, m), 2.78-2.86

(2H, m), 3.04 (2H, br d, 11.8 Hz), 3.27 (2H, t,

6.1 Hz), 5.61 (1H, d, 15.2 Hz), 5.80-5.95 (2H, m),

25 6.63-6.77 (2H, m), 7.08 (1H, s), 7.15-7.32 (4H, m).

IR (KBr): 3427, 3292, 2924, 1641, 1614, 1587, 1543, 1344, 1267, 1144, 951, 770, 702 cm⁻¹.

30 Using the above compound, the procedure of Example 1-6) was generally followed to provide the title compound as orange-colored solid.

¹H-NMR (CD₃OD) δ: 1.40-1.70 (2H, m), 1.80-2.10 (3H, m),

2.90-3.50 (8H, m), 3.69 (2H, br d, 12.8 Hz), 6.17

(1H, d, 15.4 Hz), 6.74 (1H, s), 6.80 (1H, d, 7.4

35 Hz), 7.11-7.40 (5H, m), 7.45-7.50 (1H, m), 7.55 (1H, s).

IR (KBr): 3427, 3230, 3059, 2943, 2681, 1657, 1639, 1603, 1552, 1500, 1456, 1392, 1358, 1304, 1267, 1217, 1157, 968, 839, 783, 702 cm⁻¹.

Elemental analysis for C₂₆H₃₀N₄OSCl₂•0.5H₂O

5 Calcd.: C, 59.31; H, 5.93; N, 10.64
Found : C, 59.29; H, 5.88; N, 10.59

Example 20

Synthesis of 4-(4-phenylpiperidinomethyl)-1-(5-thia-1,8b-diazaacenaphthylen-4-ylcarbonyl)piperidine dihydrochloride

The procedure of Example 4-1) was generally followed to provide 4-(4-phenylpiperidinomethyl)-1-(5-thia-1,8b-diazaacenaphthylen-4-ylcarbonyl)piperidine as red foam.

15 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.061-1.240 (2H, m), 1.672-2.103 (9H, m), 2.222 (2H, d, 6.6 Hz), 2.409-2.566 (1H, m), 2.826-2.995 (4H, m), 4.338 (2H, br d, 13.6 Hz), 5.714 (1H, dd, 1.4 Hz, 6.2 Hz), 6.061 (1H, s), 6.530-6.669 (2H, m), 6.926 (1H, s), 7.158-7.343 (5H, m).

IR (neat): 2933, 1616, 1483, 1435, 1281, 1265, 1149, 910, 771, 729, 700 cm⁻¹.

Using the above compound, the procedure of Example 1-6) was generally followed to provide the title 25 compound as orange-colored foam.

¹H-NMR (CD₃OD, 200 MHz) δ: 1.280-1.449 (2H, m), 2.002-2.321 (7H, m), 2.870-3.238 (7H, m), 3.752 (2H, br d, 12.0 Hz), 4.383 (2H, br d, 13.2 Hz), 6.528 (1H, s), 6.658 (1H, d, 7.2 Hz), 7.069 (1H, d, 9.2 Hz), 7.173-7.473 (7H, m).

IR (Nujol): 2669, 1624, 1498, 1213, 970 cm⁻¹.

Elemental analysis for C₂₇H₃₂C₁₂N₄OS•2.0H₂O

Calcd.: C, 57.14; H, 6.39; N, 9.87
Found : C, 57.02; H, 6.45; N, 9.98

35 Example 21

Synthesis of N-[[4-(4-

phenylpiperidino)cyclohexyl)methyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

The procedure of Example 11-1) was generally followed to provide N-[(4-

5 phenylpiperidino)cyclohexyl)methyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red foam.

10 $^1\text{H-NMR}$ (CDCl_3 , 200 MHz) δ : 0.842-1.071 (2H, m), 1.214-1.987 (12H, m), 2.144-2.535 (3H, m), 2.991-3.316 (4H, m), 5.716-5.771 (1H, m), 6.542-6.676 (4H, m),

6.976 (1H, s), 7.138-7.330 (5H, m).

15 IR (neat): 3307, 2927, 1616, 1551, 1510, 1483, 1279, 1153, 910, 771, 731, 700 cm^{-1} .

Using the above compound, the procedure of Example 1-6) was generally followed to provide the title 15 compound as orange-colored solid.

20 $^1\text{H-NMR}$ (CD_3OD , 200 MHz) δ : 1.048-1.246 (2H, m), 1.501-2.227 (12H, m), 2.824-2.972 (1H, m), 3.108-3.344 (4H, m), 3.533-3.675 (2H, m), 6.618 (1H, d, 8.4 Hz), 6.903-7.015 (2H, m), 7.195-7.434 (6H, m), 7.516 (1H, s).

25 IR (Nujol): 3379, 3215, 2644, 1633, 1500, 1286, 1219 cm^{-1} .

Example 22

Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

30 The procedure of Example 18-1) was generally followed to provide N-[1-(3-phenylpropan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red foam.

35 $^1\text{H-NMR}$ (CDCl_3 , 200 Mz) δ : 1.32-1.81 (5H, m), 1.81-1.97 (2H, m), 1.97-2.18 (2H, m), 2.41-2.56 (2H, m), 2.64 (2H, t, 7.6 Hz), 2.98-3.14 (2H, m), 3.19 (2H, t, 5.8 Hz), 5.76 (1H, dd, 5.6 Hz, 3.4 Hz), 6.44 (1H, t, 5.6 Hz), 6.55-6.68 (2H, m), 6.77 (1H, s), 7.02 (1H, s), 7.11-7.34 (5H, m).

IR (KBr): 3289, 1620, 1546, 1279 cm⁻¹.

Using the above compound, the procedure of Example 1-6) was generally followed to provide the title compound as orange-colored solid.

5 ¹H-NMR (DMSO-d6, 200 Mz) δ: 1.42-1.70 (3H, m), 1.72-
 1.92 (2H, m), 2.01-2.22 (2H, m), 2.62-2.78 (2H,
 m), 2.78-2.97 (2H, m), 2.97-3.33 (4H, m), 3.44-
 3.60 (2H, m), 6.66 (1H, d, 7.2 Hz), 7.03 (1H, d,
 8.8 Hz), 7.20-7.46 (2H, m), 7.71 (1H, s), 8.97
10 (1H, t, 5.4 Hz).

IR (KBr): 3379, 1641, 1535, 1294 cm⁻¹.

Elemental analysis for C₂₅H₃₀N₄OSCl₂•2H₂O

Calcd.: C, 55.45; H, 6.33; N, 10.35; Cl, 13.09

Found : C, 55.18; H, 6.29; N, 10.35; Cl, 13.05

15 Example 23

Synthesis of N-[1-(3,3'-bithiophen-5-ylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

The procedure of Example 18-1) was generally followed to provide N-[1-(3,3'-bithiophen-5-ylmethyl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as reddish brown solid.

20 ¹H-NMR (CDCl₃) δ: 1.20-1.85 (5H, m), 1.90-2.15 (2H, m),
 2.98 (2H, br d, 11.2 Hz), 3.21 (2H, t, 6.2 Hz),
25 3.71 (2H, s), 5.79 (1H, dd, 1.7 Hz, 6.3 Hz), 5.80-
 5.90 (1H, m), 6.58-6.71 (3H, m), 7.05 (1H, s),
 7.14 (1H, s), 7.20-7.40 (4H, m).

IR (KBr): 3332, 3093, 2922, 2796, 1618, 1539, 1506,
30 1481, 1367, 1340, 1277, 1155, 968, 840, 771, 737,
 594 cm⁻¹.

Using the above compound, the procedure of Example 1-6) was generally followed to provide the title compound as light orange-colored solid.

35 ¹H-NMR (CD₃OD) δ: 1.45-1.70 (2H, m), 1.80-2.10 (3H, m),
 2.95-3.40 (4H, m), 3.50-3.70 (2H, m), 4.57 (2H,
 s), 6.60 (1H, d, 7.4 Hz), 6.99 (2H, t, 4.3 Hz),

7.30-7.80 (7H, m).

IR (KBr): 3388, 3064, 2927, 2729, 1633, 1566, 1537,
1502, 1452, 1394, 1296, 939, 839, 777, 600 cm⁻¹.

Elemental analysis for C₂₅H₂₆N₄OS₃Cl₂·2.8H₂O

5 Calcd.: C, 48.74; H, 5.17; N, 9.09

Found : C, 49.10; H, 5.40; N, 8.70

Example 24

Synthesis of N-[1-(benzo[b]furan-2-ylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-

10 carboxamide dihydrochloride

The procedure of Example 18-1) was generally followed to provide N-[1-(benzo[b]furan-2-ylmethyl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as deep red foam.

15 ¹H-NMR (CDCl₃) δ: 1.25-1.80 (5H, m), 1.95-2.15 (2H, m),
2.90-3.05 (2H, m), 3.20 (2H, t, 6.0 Hz), 3.68 (2H, s),
5.79 (1H, dd, 1.7 Hz, 6.1 Hz), 5.80-5.90 (1H, m),
6.59-6.72 (4H, m), 7.05 (1H, s), 7.16-7.30 (2H, m),
7.46-7.55 (2H, m).

20 IR (KBr): 3429, 3062, 2924, 1618, 1543, 1510, 1454,
1282, 1155, 1105, 970, 773, 752 cm⁻¹.

Using the above compound, the procedure of Example 1-6) was generally followed to provide the title compound as orange-colored solid.

25 ¹H-NMR (CD₃OD) δ: 1.40-1.60 (2H, m), 1.80-2.10 (3H, m),
3.00-3.40 (4H, m), 3.50-3.70 (2H, m), 4.57 (2H, s),
6.60 (1H, d, 7.8 Hz), 6.96-7.00 (2H, m), 7.16 (1H, s),
7.26-7.42 (3H, m), 7.51-7.58 (2H, m),
7.68 (1H, d, 8.2 Hz).

30 IR (KBr): 3429, 3061, 2926, 2719, 2667, 1633, 1564,
1539, 1502, 1452, 1392, 1290, 1215, 1107, 939,
787, 756 cm⁻¹.

Elemental analysis for C₂₅H₂₆N₄O₂SCl₂·1.3H₂O

Calcd.: C, 55.51; H, 5.33; N, 10.36

35 Found : C, 55.75; H, 5.32; N, 10.36

Example 25

Synthesis of N-(1-benzhydrylpiperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

5 The procedure of Example 11-1) was generally followed to provide N-(1-benzhydrylpiperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red foam.

10 $^1\text{H-NMR}$ (CDCl_3 , 200 MHz) δ : 1.216-1.629 (5H, m), 1.809 (2H, t, 11.0 Hz), 2.882 (2H, d, 11.4 Hz), 3.175 (2H, t, 6.1 Hz), 4.224 (1H, s), 5.723 (1H, dd, 2.0 Hz, 6.0 Hz), 6.301 (1H, t, 5.7 Hz), 6.522-6.650 (3H, m), 6.967 (1H, s), 7.112-7.294 (6H, m), 7.361-7.455 (4H, m).

15 IR (neat): 3313, 2922, 1616, 1549, 1483, 1281, 1153, 908, 731, 704 cm^{-1} .

Using the above compound, the procedure of Example 1-6) was generally followed to provide the title compound as orange-colored foam.

20 $^1\text{H-NMR}$ (CD_3OD , 200 MHz) δ : 1.711-1.970 (5H, m), 3.051 (2H, br t, 12.1 Hz), 3.219 (2H, d, 5.4 Hz), 3.413 (2H, br d, 12.2 Hz), 4.910 (1H, s), 6.600 (1H, d, 7.6 Hz), 6.961-7.029 (2H, m), 7.337-7.512 (8H, m), 7.725-7.773 (4H, m).

25 IR (Nujol): 3352, 3194, 2719-2530, 1630, 1562, 1533, 1290, 1213, 754, 708 cm^{-1} .

Elemental analysis for $\text{C}_{29}\text{H}_{30}\text{C}_{12}\text{N}_4\text{OS} \cdot 1.5\text{H}_2\text{O}$

Calcd.: C, 60.00; H, 5.73; N, 9.65
Found : C, 60.00; H, 6.11; N, 9.43

Example 26

30 Synthesis of N-[4-(4-phenylpiperidin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[4-(4-phenylpiperidin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

35 To a suspension of 1.0 g (4.58 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 1.05 g (9.12

mM) of N-hydroxysuccinimide in acetonitrile (10 ml) was added 1.76 g (9.18 mM) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride at room temperature and the mixture was stirred at the prevailing temperature for 2 hours. To this reaction mixture was added a solution of 1.60 g (6.89 mM) of 1-(4-aminobutan-1-yl)-4-phenylpiperidine and 1.3 ml (9.33 mM) of triethylamine in acetonitrile (5 ml) and the mixture was further stirred for one hour. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. This crude product was purified by column chromatography (methanol/ethyl acetate 20-50-80%) to provide the title compound as red-purple solid.

Yield 1.76 g (89%)

¹H-NMR (200 MHz, CDCl₃) δ: 1.50-1.68 (m, 4H), 1.73-1.92 (m, 4H), 1.99-2.18 (m, 2H), 2.36-2.57 (m, 3H), 3.03-3.16 (m, 2H), 3.25-3.39 (m, 2H), 5.73 (dd, J=1.6, 6.0, 1H), 6.50-6.72 (m, 4H), 6.98 (s, 1H), 7.10-7.29 (m, 5H).

2) Synthesis of N-[4-(4-phenylpiperidin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 1.76 g (4.07 mM) of N-[4-(4-phenylpiperidin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (15 ml) was added 6 ml (24 mM) of 4N-HCl/methanol at room temperature and the mixture was stirred at the same temperature for several minutes. The solvent was then distilled off under reduced pressure and diethyl ether was added to the residue. The resulting crystals were collected by filtration and rinsed with diethyl ether to provide the title compound as orange-colored crystals.

Yield 1.78 g (81%)

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.42-1.61 (m, 2H), 1.65-1.86 (m, 2H), 1.87-2.26 (m, 4H), 2.73-3.31 (m, 7H), 3.28-3.61 (m, 2H), 6.61 (d, J=7.2 Hz, 1H), 6.98 (d, J=8.4 Hz, 1H), 7.17-7.40 (m, 7H), 7.65 (s, 1H), 8.84-8.97 (m, 1H).

IR (KBr): 1635, 1568, 1533, 1500, 1294, 1217, 787 cm⁻¹.

Elemental analysis for C₂₅H₃₀N₄OSCl₂·2.3H₂O

Calcd.: C, 54.90; H, 6.38; N, 10.24

10 Found : C, 54.97; H, 6.37; N, 10.16

Example 27

Synthesis of N-[3-(4-phenylpiperidin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

15 1) The procedure of Example 26-1) was generally followed to provide N-[3-(4-phenylpiperidin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple solid.

¹H-NMR (200 MHz, CDCl₃) δ: 1.63-12.19 (m, 8H), 2.55-2.60 (m, 3H), 3.10-3.23 (m, 2H), 3.37-3.49 (m, 2H), 5.57 (dd, J=1.2, 6.6 Hz, 1H), 6.47-6.65 (m, 3H), 6.67 (s, 1H), 6.91 (s, 1H), 7.16-7.35 (m, 5H).

20 2) The procedure of Example 26-2) was generally followed to provide N-[3-(4-phenylpiperidin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.82-2.23 (m, 6H), 2.72-3.34 (m, 7H), 3.46-3.61 (m, 2H), 6.58 (d, J=7.2 Hz, 1H), 6.96 (d, J=8.8 Hz, 1H), 7.16-7.40 (m, 7H), 7.63 (s, 1H), 8.92-9.04 (m, 1H).

IR (KBr): 1635, 1566, 1533, 1500, 1294, 1213, 785 cm⁻¹.

Elemental analysis for C₂₄H₂₈N₄OSCl₂·3.0H₂O

Calcd.: C, 52.84; H, 6.28; N, 10.27

35 Found : C, 52.78; H, 6.08; N, 10.05

Example 28

Synthesis of N-[4-(4-benzylpiperidin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[4-(4-benzylpiperidin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a suspension of 1.0 g (4.58 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 1.05 g (9.12 mM) of N-hydroxysuccinimide in acetonitrile (10 ml) was added 1.76 g (9.18 mM) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride at room temperature and the mixture was stirred at the prevailing temperature for 2 hours. To this reaction mixture was added a suspension of 2.19 g (6.86 mM) of 1-(4-aminobutan-1-yl)-4-benzylpiperidine dihydrochloride and 3.87 ml (27.8 mM) of triethylamine in acetonitrile (5 ml) and the mixture was further stirred for one hour. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over MgSO₄, and purified by column chromatography (methanol/ethyl acetate 30-50%) to provide the title compound as red-purple amorphous substance.

25 Yield 2.00 g (98%)

¹H-NMR (200 MHz, CDCl₃) δ: 1.51-1.92 (m, 9H), 2.23-2.43 (m, 2H), 2.53-2.78 (m, 4H), 3.22-3.42 (m, 4H), 5.72 (dd, J=2.2, 5.8 Hz, 1H), 6.52-6.62 (m, 2H), 6.94 (s, 1H), 7.04 (s, 1H), 7.10-7.48 (m, 6H).

30 2) Synthesis of N-[4-(4-benzylpiperidin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 2.00 g (4.48 mM) of N-[4-(4-benzylpiperidin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (20 ml) was added 10 ml (40 mM) of 4N-HCl/methanol at room

temperature and the mixture was stirred at room temperature for several minutes. After the solvent was distilled off under reduced pressure, diethyl ether was added to the residue and the mixture was cooled to 0°C.

5 The resulting crystals were collected by filtration and rinsed with ethanol and diethyl ether to provide the title compound as orange-colored crystals.

Yield 1.76 g (70%)

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.34-1.86 (m, 9H), 2.61-10 3.50 (m, 10H), 6.64 (d, J=7.4 Hz, 1H), 6.99 (d, J=9.0 Hz, 1H), 7.17-7.35 (m, 7H), 7.67 (s, 1H), 8.89-9.02 (m, 1H).

IR (KBr): 1635, 1566, 1533, 1500, 1294, 1215, 787 cm⁻¹.

Elemental analysis for C₂₆H₃₂N₄OSCl₂·2.3H₂O

15 Calcd.: C, 55.67; H, 6.58; N, 9.99

Found : C, 55.75; H, 6.74; N, 9.84

Example 29

Synthesis of N-[3-(4-benzylpiperidin-1-yl)propan-1-yl]-20 5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[3-(4-benzylpiperidin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a suspension of 1.0 g (4.58 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 1.05 g (9.12 mM) of N-hydroxysuccinimide in acetonitrile (10 ml) was added 1.76 g (9.18 mM) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride at room temperature and the mixture was stirred at the prevailing temperature for 2 hours. To this mixture was added a suspension of 2.09 g (6.85 mM) of 1-(3-aminopropan-1-yl)-4-benzylpiperidine dihydrochloride and 3.87 ml (27.8 mM) of triethylamine in acetonitrile (5 ml) and the mixture was further stirred for 30 minutes. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with chloroform. The organic layer was

washed with saturated aqueous solution of sodium chloride, dried over MgSO₄, and purified by column chromatography (methanol/ethyl acetate 20-40-60%) to provide the title compound as red-purple amorphous substance.

5 Yield 1.84 g (93%)

¹H-NMR (200 MHz, CDCl₃) δ: 1.22-2.05 (m, 9H), 2.45-2.57 (m, 4H), 2.93-3.10 (m, 2H), 3.34-3.46 (m, 2H), 5.75 (dd, J=2.0, 6.0 Hz, 1H), 6.54-6.67 (m, 3H), 10 7.03 (s, 1H), 7.06-7.34 (m, 5H), 8.32-8.46 (m, 1H).

15 2) Synthesis of N-[3-(4-benzylpiperidin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 1.84 g (4.25 mM) of N-[3-(4-benzylpiperidin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (10 ml) was added 6 ml (24 mM) of 4N-HCl/methanol at room temperature and the mixture was stirred at room temperature for several minutes. After the solvent was distilled off under reduced pressure, ethanol and diethyl ether were added to the crystalline residue. The crystal crop was then harvested by filtration and rinsed with ethanol and diethyl ether to provide the title compound as orange-colored crystals.

25 Yield 1.81 g (84%)

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.37-1.96 (m, 7H), 2.59-3.47 (m, 10H), 6.56 (d, J=6.8 Hz, 1H), 6.94 (d, J=8.4 Hz, 1H), 7.14-7.37 (m, 7H), 7.61 (s, 1H), 30 8.90-9.04 (m, 1H).

IR (KBr): 1633, 1568, 1300, 1217, 787 cm⁻¹.

Example 30

Synthesis of N-[4-(4-phenyl-1-piperazinyl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride

35 1) Synthesis of N-[4-(4-phenyl-1-piperazinyl)butan-1-

yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a suspension of 1.0 g (4.58 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 0.90 g (7.82 mM) of N-hydroxysuccinimide in acetonitrile (10 ml) was added 1.51 g (7.88 mM) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride at room temperature and the mixture was stirred at the prevailing temperature for 2 hours. To this reaction mixture was added a solution of 2.02 g (5.89 mM) of 1-(4-aminobutan-1-yl)-4-phenylpiperazine trihydrochloride and 4.1 ml (29.4 mM) of triethylamine in ethanol (10 ml) and the mixture was further stirred for one hour. The solvent was distilled off under reduced pressure and the residue was diluted with water and extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over MgSO₄, and purified by column chromatography (methanol/ethyl acetate 50% methanol-chloroform = 1:10). After concentration, ethanol was added to the residue and the resulting crystal crop was harvested by filtration to provide the title compound as rouge-colored crystals.

Yield 1.37 g (69%)

¹H-NMR (200 MHz, CDCl₃) δ: 1.48-1.67 (m, 4H), 2.36-2.48 (m, 2H), 2.57-2.66 (m, 4H), 3.17-3.40 (m, 6H), 5.73 (dd, J=1.6, 6.4 Hz, 1H), 6.28-6.40 (m, 1H), 6.56-6.69 (m, 3H), 6.82-6.99 (m, 4H), 7.22-7.33 (m, 2H).

IR (KBr): 3267, 3054, 3949, 2816, 1612, 1547, 1495, 1279, 1232, 1147, 761 cm⁻¹.

2) Synthesis of N-[4-(4-phenyl-1-piperazinyl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride

To a solution of 1.37 g (3.16 mM) of N-[4-(4-phenyl-1-piperazinyl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (20 ml)

was added 10 ml (40 mM) of 4N-HCl/methanol at room temperature and the mixture was stirred at room temperature for 3 hours (crystals separated out). After the solvent was distilled off under reduced pressure, ethanol and diethyl ether were added to the residue and the resulting crystals were collected by filtration and rinsed with ethanol and diethyl ether to provide the title compound.

5 Orange-colored crystals. Yield 1.7252 g (97%)

10 $^1\text{H-NMR}$ (200 MHz, DMSO-d₆) δ: 1.40-1.62 (m, 2H), 1.64-1.87 (m, 2H), 2.96-3.28 (m, 8H), 3.46-3.59 (m, 2H), 3.70-3.89 (m, 2H), 6.69 (d, J=7.0 Hz, 1H), 6.87 (d, J=7.2 Hz, 1H), 6.99-7.04 (m, 3H), 7.23-7.40 (m, 4H), 7.72 (s, 1H), 8.92-9.07 (m, 1H), 15 10.90-11.11 (m, 1H).

IR (KBr): 3404, 2914, 2503, 1635, 1566, 1533, 1497, 1441, 1288, 1215, 779 cm⁻¹.

Elemental analysis for C₂₄H₃₀N₅OSCl₃•1.0H₂O

20 Calcd.: C, 51.39; H, 5.75; N, 12.48

 Found : C, 51.37; H, 5.86; N, 12.23

Example 31

Synthesis of N-[3-(4-phenyl-1-piperazinyl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride

25 1) The procedure of Example 30-1) was generally followed to provide N-[3-(4-phenyl-1-piperazinyl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple solid.

1¹H-NMR (200 MHz, CDCl₃) δ: 1.58-1.84 (m, 2H), 2.54-2.66

30 (m, 2H), 2.66-2.77 (m, 4H), 3.26-3.38 (m, 4H), 3.38-3.53 (m, 2H), 5.37 (d, J=7.0 Hz, 1H), 6.42 (dd, J=7.0, 9.2 Hz, 1H), 6.60 (dd, J=0.8, 9.2 Hz, 1H), 6.72 (s, 1H), 6.86 (s, 1H), 6.87-6.99 (m, 3H), 7.20-7.35 (m, 2H), 8.10-8.23 (m, 1H).

35 IR (KBr): 3177, 2949, 2831, 1643, 1606, 1495, 1279, 1238, 1149, 768, 687 cm⁻¹.

2) The procedure of Example 30-2) was generally followed to provide N-[3-(4-phenyl-1-piperazinyl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride as
5 orange-colored crystals.

10 $^1\text{H-NMR}$ (200 MHz, DMSO- d_6) δ : 1.82-2.03 (m, 2H), 2.98-3.30 (m, 8H), 3.44-3.60 (m, 2H), 3.71-3.90 (m, 2H), 6.59 (d, $J=7.0$ Hz, 1H), 6.81-7.04 (m, 4H), 7.15-7.33 (m, 4H), 7.64 (m, 1H), 8.94-9.07 (m, 1H), 10.86-11.02 (m, 1H).

15 IR (KBr): 3248, 3035, 2673, 2565, 1639, 1531, 1502, 1446, 1394, 1296, 1215 cm^{-1} .

Example 32

15 Synthesis of N-[4-(4-benzyl-1-piperazinyl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride

20 1) The procedure of Example 30-1) was generally followed to provide N-[4-(4-benzyl-1-piperazinyl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red amorphous substance.

25 $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 1.48-1.65 (m, 4H), 2.31-2.63 (m, 10H), 3.23-3.36 (m, 2H), 3.51 (s, 2H), 5.77 (dd, $J=1.2$, 6.2 Hz, 1H), 6.43-6.53 (m, 1H), 6.56-6.71 (m, 3H), 7.02 (s, 1H), 7.23-35 (m, 5H).

30 2) The procedure of Example 30-2) was generally followed to provide N-[4-(4-benzyl-1-piperazinyl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride as orange-colored crystals.

35 $^1\text{H-NMR}$ (200 MHz, DMSO- d_6) δ : 1.41-1.79 (m, 4H), 3.01-4.41 (m, 14H), 6.56 (d, $J=7.4$ Hz, 1H), 6.94 (d, $J=8.8$ Hz, 1H), 7.12 (br s, 1H), 7.16-7.28 (m, 1H), 7.38-7.65 (m, 6H), 8.72-8.86 (m, 1H). IR (KBr): 3253, 2951, 2519, 1630, 1529, 1450, 1304, 1217, 791 cm^{-1} .

Elemental analysis for $C_{25}H_{32}N_5OSCl_3 \cdot 1.0H_2O$

Calcd.: C, 52.22; H, 5.96; N, 12.18

Found : C, 52.07; H, 6.05; N, 11.88

Example 33

5 Synthesis of N-[3-(4-benzyl-1-piperazinyl)propan-1-yl]-
5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydro-
chloride

10 1) The procedure of Example 30-1) was generally
followed to provide N-[3-(4-benzyl-1-
10 piperazinyl)propan-1-yl]-5-thia-1,8b-
diazaacenaphthylene-4-carboxamide as red amorphous
substance.

15 1H -NMR (200 MHz, CDCl₃) δ: 1.57-1.78 (m, 2H), 2.38-2.71
(m, 10H), 3.35-3.46 (m, 2H), 3.50 (s, 2H), 5.76
(dd, J=2.0, 6.0 Hz, 1H), 6.56-6.68 (m, 3H), 7.04
(s, 1H), 7.23-7.36 (m, 5H), 8.15-8.27 (m, 1H).
IR (KBr): 3346, 2941, 2812, 1622, 1545, 1279, 1149, 739
cm⁻¹.

20 2) The procedure of Example 30-2) was generally
followed to provide N-[3-(4-benzyl-1-
piperazinyl)propan-1-yl]-5-thia-1,8b-
diazaacenaphthylene-4-carboxamide trihydrochloride as
reddish orange-colored crystals.

25 1H -NMR (200 MHz, DMSO-d₆) δ: 1.80-2.01 (m, 2H), 3.03-
3.32 (m, 2H), 3.32-3.82 (m, 10H), 4.35-4.51 (m,
2H), 6.64 (d, J=7.4 Hz, 1H), 6.99 (d, J=9.2 Hz,
1H), 7.20 (br s, 1H), 7.31 (dd, J=7.4, 9.2 Hz,
1H), 7.42-7.55 (m, 3H), 7.61-7.76 (m, 3H), 8.93-
9.09 (m, 1H).

30 IR (KBr): 3396, 3053, 2649, 2561, 1635, 1444, 1296,
1213, 945, 791 cm⁻¹.

Elemental analysis for $C_{24}H_{30}N_5OSCl_3 \cdot 2.0H_2O$

Calcd.: C, 49.79; H, 5.92; N, 12.10

Found : C, 49.66; H, 5.80; N, 12.09

35 Example 34

Synthesis of N-[4-(1,2,3,4-tetrahydroisoquinolin-2-yl)-

butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[4-(1,2,3,4-tetrahydroisoquinolin-2-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a suspension of 1.0 g (4.58 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 1.05 g (9.12 mM) of N-hydroxysuccinimide in acetonitrile (10 ml) was added 1.76 g (9.18 mM) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride at room temperature and the mixture was stirred at the prevailing temperature for 2 hours. To this reaction mixture was added a solution of 1.90 g (6.85 mM) of 2-(4-aminobutan-1-yl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride and 4.0 ml (28.7 mM) of triethylamine in ethanol (10 ml) and the mixture was further stirred for one hour. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with methylene chloride. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over MgSO₄, and purified by column chromatography (methanol/ethyl acetate 30%) to provide the title compound as red-purple amorphous substance.

25 Yield 1.76 g (95%)

¹H-NMR (200 MHz, CDCl₃) δ: 1.57-1.92 (m, 4H), 2.58 (t, J=6.2 Hz, 2H), 2.73-2.79 (m, 2H), 2.95 (t, J=5.8 Hz, 2H), 3.25-3.37 (m, 2H), 3.69 (s, 2H), 5.55 (dd, J=2.0, 6.2 Hz, 1H), 6.30 (s, 1H), 6.48-6.60 (m, 3H), 6.97-7.16 (m, 4H), 7.41-7.55 (m, 1H).

30 2) Synthesis of N-[4-(1,2,3,4-tetrahydroisoquinolin-2-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 1.76 g (4.35 mM) of N-[4-(1,2,3,4-tetrahydroisoquinolin-2-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (10

ml) was added 6 ml (24 mM) of 4N-HCl/methanol at room temperature and the mixture was stirred at room temperature for several minutes. After the solvent was distilled off under reduced pressure, ethanol was added
5 to the residue and the mixture was concentrated. Then, diethyl ether was added and the crystal crop was harvested by filtration and rinsed with ethanol and diethyl ether to provide the title compound.

Orange-colored crystals. Yield 1.65 g (78%)
10 $^1\text{H-NMR}$ (200 MHz, DMSO-d₆) δ: 1.42-1.62 (m, 2H), 1.70-1.93 (m, 2H), 2.91-3.39 (m, 7H), 3.56-3.77 (m, 1H), 4.18-4.35 (m, 1H), 4.43-4.59 (m, 1H), 6.57 (d, J=6.8 Hz, 1H), 6.95 (d, J=8.4 Hz, 1H), 7.09-7.32 (m, 6H), 7.61 (s, 1H), 8.83-8.95 (m, 1H).
15 IR (KBr): 3400, 3045, 2939, 1635, 1562, 1535, 1500, 1440, 1292, 1211, 756 cm⁻¹.

Elemental analysis for C₂₃H₂₆N₄OSCl₂•0.5H₂O

Calcd.: C, 56.79; H, 5.59; N, 11.52

Found : C, 56.67; H, 5.73; N, 11.40

20 Example 35

Synthesis of N-[3-(1,2,3,4-tetrahydroisoquinolin-2-yl)-propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) The procedure of Example 34-1) was generally followed to provide N-[3-(1,2,3,4-tetrahydroisoquinolin-2-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

30 $^1\text{H-NMR}$ (200 MHz, CDCl₃) δ: 1.65-1.90 (m, 2H), 2.67-2.83 (m, 4H), 2.93-3.03 (m, 2H), 3.39-3.52 (m, 2H), 3.71 (s, 2H), 5.23 (dd, J=1.6, 6.6 Hz, 1H), 6.13 (s, 1H), 6.31 (s, 1H), 6.44-6.53 (m, 2H), 6.97-7.13 (m, 4H), 8.71-8.94 (m, 1H).

35 2) The procedure of Example 34-2) was generally followed to provide N-[3-(1,2,3,4-tetrahydroisoquinolin-2-yl)propan-1-yl]-5-thia-1,8b-

diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

5 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.88-2.12 (m, 2H), 2.88-3.36 (m, 7H), 3.56-3.75 (m, 1H), 4.17-4.37 (m, 1H), 4.45-4.60 (m, 1H), 6.59 (d, J=7.4 Hz, 1H), 6.96 (d, J=9.0 Hz, 1H), 7.14-7.35 (m, 6H), 7.64 (s, 1H), 8.96-9.11 (m, 1H).
IR (KBr): 3390, 3047, 295, 2684, 2600, 1637, 1531, 1442, 1294, 1211 cm⁻¹.

10 Example 36

Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

15 1) Synthesis of N-(1-ethoxycarbonylpiperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene carboxamide

To a suspension of 10.76 g (38.45 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid hydrochloride and 11.35 g (98.62 mM) of N-hydroxysuccinimide in acetonitrile (150 ml) was added 20 18.9 g (98.59 mM) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride and the mixture was stirred at room temperature for 2 hours. Then, at room temperature, a solution of 10 ml (58.3 mM) of ethyl 4-aminopiperidine-1-carboxylate and 13 ml (92.3 mM) of triethylamine in acetonitrile (30 ml) was added and the mixture was stirred for 2 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with chloroform. The organic layer was washed with 25 saturated aqueous solution of sodium chloride and dried over MgSO₄. The crude product thus obtained was purified by column chromatography (methanol/ethyl acetate 20%) to provide the title compound.

Red amorphous substance. Yield 19.47 g (quantitative)
35 ¹H-NMR (200 MHz, CDCl₃) δ: 1.16-1.46 (m, 2H), 1.26 (t, J=7.0 Hz, 3H), 1.93-2.02 (m, 2H), 2.84-2.97 (m,

2H), 3.87-4.21 (m, 3H), 4.13 (q, J=7.0 Hz, 2H),
5.67 (br d, J=8.0 Hz, 1H), 5.80 (dd, J=1.8, 6.2
Hz, 1H), 6.59-6.71 (m, 3H), 7.05 (s, 1H).

5 2) Synthesis of N-(1-tert-butoxycarbonylpiperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene carboxamide

Under argon gas, 21 ml (147.6 mM) of trimethylsilyl iodide was added to a solution of 19.47 g (<38.45 mM) of N-(1-ethoxycarbonylpiperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene carboxamide in acetonitrile (350 ml) at room temperature and the mixture was stirred for 84 hours. The reaction was stopped by adding methanol to the reaction system and 30 ml (215 mM) of triethylamine and 9.8 ml (42.7 mM) of di-tert-butyl dicarbonate were added at room temperature, followed by 1 hour of stirring. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The crude product thus obtained was purified by column chromatography (methanol/ethyl acetate 20%) to provide the title compound as red amorphous substance (14.59 g, 95%).

20 ¹H-NMR (200 MHz, CDCl₃) δ: 1.13-1.99 (m, 2H), 1.46 (s, 9H), 1.73-1.98 (m, 2H), 2.74-2.95 (m, 2H), 3.84-4.18 (m, 3H), 5.70-5.85 (m, 1H), 5.79 (dd, J=1.9, 5.7 Hz, 1H), 6.58-6.72 (m, 3H), 7.04 (s, 1H).

25 3) Synthesis of N-(piperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene carboxamide dihydrochloride

30 To 14.59 g (36.4 mM) of N-(1-tert-butoxycarbonylpiperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene carboxamide was added 20 ml (240 mM) of 12N-hydrochloric acid at room temperature and the mixture was stirred at room temperature for one hour. To this reaction mixture was added ethanol and the resulting crystal crop was harvested by filtration and

rinsed with ethanol and diethyl ether to provide the title compound.

Orange-colored crystals. Yield 10.08 g (74%)

¹H-NMR (200 MHz, D₂O) δ: 1.64-1.87 (m, 2H), 2.03-2.19
5 (m, 2H), 3.03-3.21 (m, 2H), 3.42-3.58 (m, 2H),
3.82-4.02 (m, 1H), 5.98 (d, J=7.0 Hz, 1H), 6.60
(d, J=9.2 Hz, 1H), 6.67 (s, 1H), 6.78 (dd, J=7.2,
9.2 Hz, 1H), 6.98 (s, 1H).

IR (KBr): 3481, 3223, 2935, 2798, 2717, 1633, 1529
10 1302, 1257, 1211, 787 cm⁻¹.

4) Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a solution of 0.40 g (1.07 mM) of N-(piperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene carboxamide dihydrochloride and 0.75 ml (5.38 mM) of triethylamine in ethanol (5 ml) was added 0.20 ml (1.32 mM) of 1-bromo-3-phenylpropane at room temperature and the mixture was refluxed under nitrogen for 15 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with methylene chloride. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over MgSO₄, and purified by column chromatography (methanol/ethyl acetate 20-40%) to provide the title compound.

Red-purple amorphous substance. Yield 356 mg (80%)

¹H-NMR (200 MHz, CDCl₃) δ: 1.41-1.64 (m, 2H), 1.75-2.21
(m, 6H), 2.31-2.47 (m, 2H), 2.63 (t, J=7.7 Hz,
2H), 7.79-2.96 (m, 2H), 3.72-3.92 (m, 1H), 5.75-
30 5.80 (m, 2H), 6.57-6.69 (m, 3H), 7.03 (s, 1H),
7.16-7.32 (m, 5H).

5) Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

35 To a solution of 356.2 mg (0.85 mM) of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaace-

naphthylene-4-carboxamide in ethanol (6 ml) was added 2.0 ml (8.0 mM) of 4N-HCl/methanol at room temperature and the mixture was stirred at room temperature for several minutes. After the solvent was distilled off 5 under reduced pressure, diethyl ether was added to the residue and the resulting crystals were collected by filtration and rinsed with ethanol and diethyl ether to provide the title compound.

Orange-colored crystals. Yield 399 mg (96%)
10 $^1\text{H-NMR}$ (200 MHz, DMSO-d₆) δ : 1.80-2.14 (m, 6H), 2.63 (t, J=7.5 Hz, 2H), 2.82-3.11 (m, 4H), 3.38-3.56 (m, 2H), 3.72-3.93 (m, 1H), 6.64 (d, J=6.6 Hz, 1H), 6.99 (d, J=9.2 Hz, 1H), 7.15-7.38 (m, 7H), 7.67 (s, 1H), 8.80-8.90 (m, 1H).
15 IR (KBr): 3412, 3051, 1635, 1564, 1535, 1495, 1304 cm⁻¹.

Elemental analysis for C₂₄H₂₈N₄OSCl₂·2.5H₂O

Calcd.: C, 53.73; H, 6.20; N, 10.44
Found : C, 54.03; H, 5.96; N, 10.46

20 Example 37

Synthesis of N-(1-phenethylpiperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride
1) The procedure of Example 36-4) was generally followed to provide N-(1-phenethylpiperidin-4-yl)-5-25 thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple solid.

m.p. 216.0-217.0°C
1¹ H-NMR (200 MHz, CDCl₃) δ : 1.40-1.70 (2H, m), 1.80-2.20 (4H, m), 2.50-3.10 (6H, m), 3.70-4.00 (1H, m), 30 5.60-5.90 (2H, m), 6.50-6.80 (3H, m), 7.04 (1H, s), 7.10-7.40 (5H, m).
IR (KBr): 3292, 2947, 1612, 1537, 1279, 1159, 771, 735, 696 cm⁻¹.

2) The procedure of Example 36-5) was generally followed to provide N-(1-phenethylpiperidin-4-yl)-5-35 thia-1,8b-diazaacenaphthylene-4-carboxamide

dihydrochloride as orange-colored crystals.

¹H-NMR (200 MHz, CD₃OD) δ: 1.80-2.30 (m, 6H), 3.00-3.60
(m, 4H), 3.73 (br d, J=12.8 Hz, 2H), 3.90-4.20 (m,
1H), 6.61 (d, J=7.0 Hz, 1H), 6.90-7.10 (m, 2H),
5 7.20-7.50 (m, 6H), 7.53 (s, 1H).

IR (KBr): 3427, 3244, 3030, 2935, 2727, 1632, 1562,
1537, 1502, 1458, 1308, 791, 758, 704 cm⁻¹.

Elemental analysis for C₂₃H₂₆N₄OSCl₂·1.0H₂O

Calcd.: C, 55.76; H, 5.70; N, 11.31

10 Found : C, 56.06; H, 5.47; N, 11.51

Example 38

Synthesis of N-[1-[3-(2-fluorophenyl)propan-1-yl]-
piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-
carboxamide dihydrochloride

15 1) Synthesis of N-[1-[3-(2-fluorophenyl)propan-1-yl]-
piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-
carboxamide

To a solution of 616.7 mg (4.0 mM) of 3-(2-fluoro-
phenyl)propanol and 809.5 mg (8.0 mM) of triethylamine
20 in ether (20 ml) was added 687.3 mg (6.0 mM) of
methanesulfonyl chloride gradually with ice-cooling and
the mixture was stirred at the prevailing temperature
for 5 minutes and, then at room temperature for 1 hour.
Then, 405 mg (4.0 mM) of triethylamine and 344 mg (3.0
25 mM) of methanesulfonyl chloride were further added and
the mixture was further stirred at room temperature for
1 hour. To this reaction mixture was added 5% aqueous
solution of sodium hydrogen carbonate and the reaction
product was extracted into ethyl acetate. The organic
30 layer was washed with water and dried over Na₂SO₄ and
the solvent was distilled off under reduced pressure.
To the mesyl compound thus obtained was added a
solution of 746.6 mg (2.0 mM) of N-(piperidin-4-yl)-5-
thia-1,8b-diazaacenaphthylene carboxamide
35 dihydrochloride and 1.15 g (10 mM) of triethylamine in
ethanol (10 ml) and the mixture was refluxed overnight.

To this reaction mixture was added 5% aqueous solution of sodium hydrogen carbonate and the reaction product was extracted into ethyl acetate. The organic layer was washed with water and dried over Na_2SO_4 and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol = 3/1). After concentration, ether was added to the residue and the resulting crystals were collected by filtration to provide the title compound as reddish orange-colored solid (553.6 mg, 63.4%).

$^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 1.35-1.57 (2H, m), 1.70-2.15 (6H, m), 2.40 (2H, t, $J=7.5$ Hz), 2.66 (2H, t, $J=8.0$ Hz), 2.85 (2H, br d, $J=12.0$ Hz), 3.70-3.90 (1H, m), 5.67 (1H, d, $J=7.8$ Hz), 5.78 (1H, dd, $J=1.5$, 6.1 Hz), 6.58-6.70 (3H, m), 6.95-7.22 (5H, m).

IR (KBr): 3429, 3394, 3217, 3049, 2939, 2804, 2771, 1632, 1614, 1552, 1512, 1479, 1454, 1311, 1281, 1246, 1228, 1140, 1099, 781, 758, 735 cm^{-1} .

2) Synthesis of N-[1-{3-(2-fluorophenyl)propan-1-yl}-piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 553.6 mg (1.3 mM) of N-[1-{3-(2-fluorophenyl)propan-1-yl}piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (20 ml) was added 2 ml (8.0 mM) of 4N-HCl/ethyl acetate and the mixture was stirred for several minutes. The solvent was then distilled off under reduced pressure and ether was added to the residue. The resulting crystal crop was harvested by filtration to provide orange-colored crystals (666.6 mg, 94%).

$^1\text{H-NMR}$ (200 MHz, CD_3OD) δ : 1.80-2.20 (m, 6H), 2.77 (t, $J=7.4$ Hz, 2H), 3.00-3.22 (m, 3H), 3.40-3.50 (m, 1H), 3.63 (br d, $J=12.4$ Hz, 2H), 3.90-4.10 (m, 1H), 6.61 (d, $J=7.6$ Hz, 1H), 6.98-7.43 (m, 7H),

7.53 (s, 1H).

IR (KBr): 3427, 3390, 3062, 2940, 2717, 1633, 1564,
1539, 1504, 1456, 1304, 1217, 771 cm⁻¹.

Elemental analysis for C₂₄H₂₇N₄OSCl₂·2H₂O

5 Calcd.: C, 52.84; H, 5.73; N, 10.27

Found : C, 52.66; H, 5.83; N, 10.20

Example 39

Synthesis of N-[1-[3-(2-chlorophenyl)propan-1-yl]-
10 piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-
carboxamide dihydrochloride

1) The procedure of Example 38-1) was generally
followed to provide N-[1-[3-(2-chlorophenyl)propan-1-
yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-
carboxamide as red solid.

15 ¹H-NMR (200 MHz, CDCl₃) δ: 1.39-1.59 (2H, m), 1.73-2.16
(6H, m), 2.40 (2H, t, J=7.5 Hz), 2.75 (2H, t,
J=7.7 Hz), 2.86 (2H, br d, J=12.2 Hz), 3.70-3.95
(1H, m), 5.64 (1H, d, J=7.6 Hz), 5.79 (1H, dd,
J=1.8, 6.2 Hz), 6.58-6.70 (3H, m), 7.05 (1H, s),
20 7.10-7.36 (4H, m).

IR (KBr): 3230, 2949, 1633, 1614, 1541, 1508, 1479,
1311, 1281, 1246, 1140, 779, 758 cm⁻¹.

2) The procedure of Example 38-2) was generally
followed to provide N-[1-[3-(2-chlorophenyl)propan-1-
25 yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-
carboxamide dihydrochloride as reddish orange-colored
crystals.

30 ¹H-NMR (200 MHz, CD₃OD) δ: 1.80-2.20 (6H, m), 2.82-2.90
(2H, m), 3.03-3.22 (3H, m), 3.40-3.50 (1H, m),
3.65 (2H, br d, J=12.2 Hz), 3.90-4.10 (1H, m),
6.61 (1H, d, J=7.2 Hz), 6.97-7.04 (2H, m), 7.19-
7.43 (5H, m), 7.53 (1H, s).

IR (KBr): 3400, 3066, 2945, 2717, 1633, 1568, 1539,
1504, 1473, 1456, 1302, 1215, 758 cm⁻¹.

35 Elemental analysis for C₂₄H₂₇N₄OSCl₂·2H₂O

Calcd.: C, 51.30; H, 5.56; N, 9.97

Found : C, 51.47; H, 5.69; N, 9.87

Example 40

Synthesis of N-[1-[2-(thiophen-3-yl)ethan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

5 1) The procedure of Example 38-1) was generally followed to provide N-[1-[2-(thiophen-3-yl)ethan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as rouge-colored solid.

10 ¹H-NMR (200 MHz, CDCl₃) δ: 1.40-1.60 (2H, m), 1.90-2.05 (2H, m), 2.12-2.23 (2H, m), 2.58-2.65 (2H, m), 2.79-2.95 (4H, m), 3.75-3.95 (1H, m), 5.60-5.80 (2H, m), 6.58-6.70 (3H, m), 6.94-7.04 (3H, m), 7.23-7.25 (1H, m).

15 IR (KBr): 3292, 2949, 1608, 1539, 1508, 1481, 1308, 1279, 1236, 1161, 1119, 771, 737, 646 cm⁻¹.

20 2) The procedure of Example 38-2) was generally followed to provide N-[1-[2-(thiophen-3-yl)ethan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

25 ¹H-NMR (200 MHz, CD₃OD) δ: 1.85-2.25 (4H, m), 3.05-3.20 (4H, m), 3.23-3.50 (2H, m), 3.60-3.75 (2H, m), 3.90-4.15 (1H, m), 6.61 (1H, d, J=7.2 Hz), 6.96-7.10 (3H, m), 7.10-7.45 (3H, m), 7.52 (1H, s).

30 IR (KBr): 3392, 3059, 2910, 2721, 2675, 2551, 1633, 1564, 1529, 1502, 1458, 1394, 1304, 1263, 1215, 787 cm⁻¹.

Example 41

Synthesis of N-[1-(1,4-benzodioxan-2-ylmethyl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

35 1) The procedure of Example 38-1) was generally followed to provide N-[1-(1,4-benzodioxan-2-ylmethyl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red amorphous substance.

¹H-NMR (200 MHz, CDCl₃) δ: 1.38-1.53 (m, 2H), 1.86-2.02 (m, 2H), 2.18-2.21 (m, 2H), 2.52-2.76 (m, 2H), 2.80-3.02 (m, 2H), 23.72-3.91 (m, 1H), 3.98 (dd, J=7.6, 11.6 Hz, 1H), 4.22-4.35 (m, 2H), 5.48-5.60 (m, 1H), 5.80 (dd, J=1.6, 6.4 Hz, 1H), 6.59-6.72 (m, 3H), 6.80-6.91 (m, 4H), 7.06 (s, 1H).
IR (KBr): 1620, 1543, 1493, 1267, 1149, 782 cm⁻¹.
2) The procedure of Example 38-2) was generally followed to provide N-[1-(1,4-benzodioxan-2-ylmethyl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.
¹H-NMR (200 MHz, DMSO-d₆) δ: 1.81-2.09 (m, 4H), 2.95-4.39 (m, 9H), 4.85-5.00 (m, 1H), 6.48-6.53 (m, 1H), 6.77-6.98 (m, 5H), 7.10-7.23 (m, 2H), 7.55 (s, 1H), 8.71-8.79 (m, 1H).
IR (KBr): 1637, 1497, 1304, 1263, 762 cm⁻¹.
Elemental analysis for C₂₄H₂₆N₄O₃SCl₂•2.0H₂O
Calcd.: C, 51.71; H, 5.42; N, 10.05
Found : C, 51.74; H, 5.34; N, 9.91
Example 42.
Synthesis of N-[2-(1-(3-phenylpropan-1-yl)piperidin-4-yl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride
1) Synthesis of N-[2-(1-tert-butoxycarbonyl-4-piperidyl)ethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
In 50 ml of acetonitrile were suspended 4.37 g (20.0 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 4.60 g (40.0 mM) of N-hydroxysuccinimide, followed by addition of 7.67 g (40.0 mM) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride, and the mixture was stirred at room temperature for 1 hour.
The solvent was then distilled off under reduced pressure and the residue was extracted with chloroform.

The organic layer was washed with saturated aqueous solution of sodium chloride and dried over $MgSO_4$ and the solvent was distilled off under reduced pressure. The active ester thus obtained was dissolved in 100 ml of chloroform. To this solution were added 5.6 ml (40.0 mM) of triethylamine and 3.08 g (24.0 mM) of 4-(2-aminoethyl)piperidine, and the mixture was stirred at room temperature for 30 minutes. Then, 4.37 g (20.0 mM) of di-tert-butyl dicarbonate was added dropwise and the mixture was further stirred at room temperature for 1 hour. This reaction mixture was washed with water and the organic layer was further washed with saturated aqueous solution of sodium chloride. The organic layer was dried over $MgSO_4$ and the solvent was distilled off under reduced pressure. The residue was purified by column chromatography (ethyl acetate/ethanol = 10/1) to provide the title compound.

Red oil. Yield 3.37 g (39%)

1H -NMR (200 MHz, $CDCl_3$) δ : 1.01-1.28 (m, 2H), 1.41-1.58 (m, 12H), 1.62-1.76 (m, 2H), 2.62-2.74 (m, 2H), 3.34 (m, 2H), 4.04-4.11 (m, 2H), 5.79 (dd, $J=2.0$, 6.0 Hz, 1H), 5.85 (t, $J=5.6$ Hz, 1H), 6.62-6.71 (m, 3H), 7.04 (s, 1H).

IR (KBr): 1684, 1622, 1547, 1281, 1159 cm^{-1} .

2) Synthesis of N-[2-(4-piperidyl)ethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 3.37 g (7.86 mM) of N-[2-(1-tert-butoxycarbonyl-4-piperidyl)ethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (100 ml) was added 12N-hydrochloric acid (3.2 ml, 39.3 mM) and the mixture was stirred at room temperature for 1 hour. The resulting crystals were collected by filtration and rinsed with small amounts of ethanol and ether to provide the title compound.

Orange-colored crystals. Yield 2.52 g (80.0%)

1H -NMR (200 MHz, $DMSO-d_6$) δ : 1.22-1.68 (m, 5H), 1.78-

1.85 (m, 2H), 2.68-2.91 (m, 2H), 3.10-3.31 (m,
4H), 6.63 (d, J=6.8 Hz, 1H), 7.00 (d, J=9.2 Hz,
1H), 7.24 (s, 1H), 7.31 (dd, J=6.8, 9.2 Hz, 1H),
7.68 (s, 1H), 8.91 (t, J=5.6 Hz, 1H), 9.08 (br s,
5 2H).

IR (KBr): 1643, 1533, 1290 cm⁻¹.

3) Synthesis of N-[2-(1-(3-phenylpropan-1-yl)piperidin-4-yl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

10 To a solution of 0.60 g (1.49 mM) of N-[2-(4-piperidyl)ethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride and 1.0 ml (7.17 mM) of triethylamine in ethanol (6 ml) was added 0.27 ml (1.78 mM) of 3-phenyl-1-bromopropane at room temperature and the mixture was refluxed under nitrogen for 24 hours.

15 The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over MgSO₄, and purified by column chromatography (methanol/ethyl acetate 30-50-80%) to provide the title compound.

20 Red-purple amorphous substance. Yield 514 mg (77%)
¹H-NMR (200 MHz, CDCl₃) δ: 1.08-2.01 (m, 11H), 2.31-
25 2.39 (m, 2H), 2.62 (t, J=7.7 Hz, 2H), 2.92 (br d,
J=11.2 H, 2H), 3.28-3.38 (m, 2H), 5.55-5.68 (m,
1H), 5.78 (dd, J=1.7, 6.5 Hz, 1H), 6.58-6.70 (m,
3H), 7.05 (s, 1H), 7.12-7.33 (m, 5H).

25 4) Synthesis of N-[2-(1-(3-phenylpropan-1-yl)piperidin-4-yl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

30 To a solution of 0.5142 g (1.15 mM) of N-[2-(1-(3-phenylpropan-1-yl)piperidin-4-yl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (10 ml) was added 4 ml (16 mM) of 4N-HCl/methanol at room temperature and the mixture was stirred at room

temperature for several minutes. The solvent was distilled off under reduced pressure and diethyl ether was added to the residue. The resulting crystals were collected by filtration and rinsed with ethanol and
5 diethyl ether to provide the title compound.

Orange-colored crystals. Yield 546 mg (88%)
¹H-NMR (200 MHz, DMSO-d₆) δ: 1.31-1.61 (m, 5H), 1.70-
2.14 (m, 4H), 2.63 (t, J=7.5 Hz, 2H), 2.70-3.23
(m, 6H), 3.36-3.52 (m, 2H), 6.59 (d, J=7.4 Hz,
10 1H), 6.96 (d, J=8.8 Hz, 1H), 7.16 (s, 1H), 7.19-
7.37 (m, 6H), 7.63 (s, 1H), 8.74-9.88 (m, 1H).
IR (KBr): 1639, 1560, 1537, 1500, 1444, 1290, 1217,
831, 785 cm⁻¹.

Elemental analysis for C₂₆H₃₂N₄OSCl₂•1.0H₂O
15 Calcd.: C, 58.09; H, 6.38; N, 10.42
Found : C, 58.22; H, 6.12; N, 10.45

Example 43

Synthesis of N-[2-(1-phenethylpiperidin-4-yl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
20 dihydrochloride

1) The procedure of Example 42-3) was generally followed to provide N-[2-(1-phenethylpiperidin-4-yl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

25 ¹H-NMR (200 MHz, CDCl₃) δ: 1.32-1.58 (m, 4H), 1.69-2.20
(m, 5H), 2.63-2.71 (m, 2H), 2.84-2.92 (m, 2H),
3.04-3.18 (m, 2H), 3.31-3.41 (m, 2H), 5.71-5.85
(m, 1H), 5.79 (dd, J=1.8, 6.2 Hz, 1H), 6.59-6.67
(m, 2H), 6.71 (s, 1H), 7.06 (s, 1H), 7.16-7.39 (m,
30 5H).

2) The procedure of Example 42-4) was generally followed to provide N-[2-(1-phenethylpiperidin-4-yl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

35 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.31-1.62 (m, 5H), 1.77-
1.96 (m, 2H), 2.72-3.30 (m, 8H), 3.46-3.60 (m,

2H), 6.61 (d, J=7.4 Hz, 1H), 6.97 (d, J=9.2 Hz, 1H), 7.17 (s, 1H), 7.20-7.42 (m, 6H), 7.65 (s, 1H), 8.80-8.90 (m, 1H).

5 IR (KBr): 1632, 1564, 1535, 1441, 1290, 1211, 795, 770 cm⁻¹.

Example 44

Synthesis of N-[2-(1-(3-(2-chlorophenyl)propan-1-yl)-piperidin-4-yl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

10 1) Synthesis of N-[2-(1-(3-(2-chlorophenyl)propan-1-yl)piperidin-4-yl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a solution of 409.5 mg (2.4 mM) of 3-(2-chlorophenyl)propanol and 0.7 ml (4.8 mM) of triethylamine in ether (20 ml) was added 412.4 mg (3.6 mM) of methanesulfonyl chloride gradually with ice-cooling and the mixture was stirred at room temperature for 2 hours. To the reaction mixture was added 5% aqueous solution of sodium hydrogen carbonate and the product was extracted into ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over Na₂SO₄ and the solvent was distilled off under reduced pressure. To the mesyl compound thus obtained was added a solution of 481.6 mg (1.2 mM) of 2-(piperidin-4-yl)ethan-1-yl-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride and 0.85 ml (6.0 mM) of triethylamine in ethanol (10 ml) and the mixture was refluxed overnight. To this reaction mixture was added 5% aqueous solution of sodium hydrogen carbonate and the reaction product was extracted into ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over Na₂SO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol = 3/1), concentrated, and treated with

ether, whereby the title compound was obtained as deep-red amorphous substance (327.9 mg, 56.8%).

5 ¹H-NMR (200 MHz, CDCl₃) δ: 1.10-1.55 (5H, m), 1.60-2.10
 (6H, m), 2.37-2.44 (2H, m), 2.74 (2H, t, J=7.6
 Hz), 2.95 (2H, br d, J=11.0 Hz), 3.28-3.38 (2H,
 m), 5.65-5.80 (1H, m), 5.78 (1H, dd, J=1.9, 6.3
 Hz), 6.60-6.70 (3H, m), 7.05 (1H, s), 7.10-7.20
 (4H, m).
10 IR (KBr): 3286, 3057, 2926, 1618, 1545, 1512, 1479,
 1442, 1280, 1153, 1053, 970, 870, 754, 677, 650
 cm⁻¹.

15 2) Synthesis of N-[2-(1-(3-(2-chlorophenyl)propan-1-yl)piperidin-4-yl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride
15 To a solution of 327.9 mg (0.68 mM) of N-[2-(1-(3-(2-chlorophenyl)propan-1-yl)piperidin-4-yl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (10 ml) was added 2 ml (8.0 mM) of 4N-HCl/ethyl acetate and the mixture was stirred for several
20 minutes. The solvent was then distilled off under reduced pressure and ether was added to the residue. The resulting crystals were collected by filtration and rinsed with ethanol and diethyl ether to provide the title compound as orange-colored crystals (364.0 mg, 91%).

25 ¹H-NMR (200 MHz, CD₃OD) δ: 1.30-1.80 (5H, m), 1.90-2.10
 (4H, m), 2.90-3.40 (8H, m), 3.50-3.70 (2H, m),
 6.60 (1H, d, J=6.8 Hz), 6.96-7.00 (2H, m), 7.10-
 7.45 (5H, m), 7.51 (1H, s).
30 IR (KBr): 3427, 3057, 2939, 2727, 1632, 1566, 1535,
 1502, 1473, 1439, 1390, 1292, 1215, 1051, 951, 762
 cm⁻¹.

Elemental analysis for C₂₆H₃₁N₄OSCl₂•2.0H₂O
Calcd.: C, 52.93; H, 5.98; N, 9.50
35 Found : C, 52.95; H, 5.75; N, 9.41

Example 45

Synthesis of N-[2-(1-(2-chlorophenethyl)piperidin-4-yl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) The procedure of Example 44-1) was generally
5 followed to provide N-[2-(1-(2-chlorophenethyl)piperidin-4-yl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as deep red amorphous substance.

¹H-NMR (200 MHz, CDCl₃) δ: 1.25-1.55 (5H, m), 1.60-1.85
10 (2H, m), 1.95-2.15 (2H, m), 2.54-2.62 (2H, m),
2.91-3.06 (4H, m), 3.30-3.40 (2H, m), 6.60-6.75
(1H, m), 5.79 (1H, dd, J=1.6, 6.0 Hz), 6.59-6.71
(3H, m), 7.05 (1H, s), 7.10-7.36 (4H, m).
IR (KBr): 3334, 3062, 2927, 1618, 1543, 1512, 1479,
15 1441, 1371, 1342, 1281, 1211, 1153, 1111, 1051,
970, 771, 752, 729 cm⁻¹.

2) The procedure of Example 44-2) was generally
followed to provide N-[2-(1-(2-chlorophenethyl)piperidin-4-yl)ethan-1-yl]-5-thia-1,8b-
20 diazaacenaphthylene-4-carboxamide dihydrochloride as
orange-colored crystals.

¹H-NMR (200 MHz, CD₃OD) δ: 1.40-1.90 (5H, m), 1.95-2.20
(2H, m), 3.00-3.40 (8H, m), 3.60-3.80 (2H, m),
6.61 (1H, d, J=7.4 Hz), 6.97-7.01 (2H, m), 7.25-
25 7.50 (5H, m), 7.52 (1H, s).
IR (KBr): 3425, 2941, 2665, 2532, 1632, 1566, 1537,
1502, 1473, 1394, 1338, 1286, 1215, 1111, 783 cm⁻¹.
Elemental analysis for C₂₅H₂₉N₄OSCl₁•1.0H₂O

Calcd.: C, 53.82; H, 5.60; N, 10.04
30 Found : C, 54.06; H, 5.66; N, 9.97

Example 46

Synthesis of N-[3-(1-(3-phenylpropan-1-yl)piperidin-4-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

35 1) Synthesis of N-[3-(1-tert-butoxycarbonyl-4-piperidyl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-

4-carboxamide

In acetonitrile (120 ml) was suspended 6.55 g (30.0 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid as well as 6.91 g (60.0 mM) of N-hydroxysuccinimide, followed by addition of 11.50 g (60.0 mM) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride, and the mixture was stirred at room temperature for 1 hour. The solvent was then distilled off under reduced pressure and the residue was extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄, and the solvent was distilled off under reduced pressure to provide the active ester. To a solution of this active ester in chloroform (100 ml) was added 8.4 ml (60.0 mM) of triethylamine as well as 8.72 g (36.0 mM) of 3-(1-tert-butoxycarbonyl-4-piperidyl)propylamine and the mixture was stirred at room temperature for 30 minutes. This reaction mixture was washed with purified water and the organic layer was further washed with saturated aqueous solution of sodium chloride. After the organic layer was dried over MgSO₄, the solvent was distilled off under reduced pressure and the residue was purified by column chromatography (ethyl acetate/ethanol = 10/1) to provide the title compound. Red solid. Yield 10.16 g (76%).

¹H-NMR (200 MHz, CDCl₃) δ: 0.95-1.41 (m, 4H), 1.45 (s, 9H), 1.48-1.72 (m, 5H), 2.61-2.73 (m, 2H), 3.28 (m, 2H), 4.05-4.14 (m, 2H), 5.79 (dd, J=2.2, 5.8 Hz, 1H), 6.02 (t, J=5.6 Hz, 1H), 6.63-6.70 (m, 3H), 7.02 (s, 1H).

IR (KBr): 1684, 1624, 1278, 1161 cm⁻¹.

2) Synthesis of N-[3-(4-piperidyl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride
To a solution of 10.12 g (22.87 mM) of N-[3-(1-tert-butoxycarbonyl-4-piperidyl)propan-1-yl]-5-thia-

1,8b-diazaacenaphthylene-4-carboxamide in 100 ml of ethanol was added 9.4 ml (114.33 mM) of 12N-hydrochloric acid and the mixture was stirred at room temperature for 1 hour. The resulting precipitate was recovered by filtration and rinsed with small amounts of ethanol and ether to provide 8.79 g (92.5%) of the title compound as orange-colored crystals.

5 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.13-1.59 (m, 7H), 1.74-
10 1.80 (m, 2H), 2.68-2.93 (m, 2H), 3.04-3.30 (m,
 4H), 6.62 (d, 1H), 7.00 (d, J=9.2 Hz, 1H), 7.18
 (s, 1H), 7.30 (dd, J=7.4, 9.2 Hz, 1H), 7.67 (s,
 1H), 8.84 (t, J=5.6 Hz, 1H), 8.88-9.15 (br s, 2H).
IR (KBr): 1637, 1564, 1518 cm⁻¹.

15 3) Synthesis of N-[3-(1-(3-phenylpropan-1-yl)piperidin-4-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

20 To a solution of 1.0 g (2.41 mM) of N-[3-(4-piperidyl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride and 1.7 ml (12.2 mM) of triethylamine in ethanol (10 ml) was added 0.45 ml (2.96 mM) of 1-bromo-3-phenylpropane at room temperature and the mixture was refluxed under nitrogen for 20 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over MgSO₄, and purified by column chromatography (methanol/ethyl acetate 30-50-100%) to provide the title compound.

25

30 Red-purple amorphous substance. Yield 811 mg (73%)

1¹H-NMR (200 MHz, CDCl₃) δ: 1.17-1.38 (m, 4H), 1.44-2.03
 (m, 9H), 2.34-2.41 (m, 2H), 2.62 (t, J=7.7 Hz,
 2H), 2.86-3.02 (m, 2H), 3.29 (q, J=6.6 Hz, 2H),
 5.61-5.73 (m, 1H), 5.79 (dd, J=1.6, 6.4 Hz, 1H),
 6.58-6.70 (m, 3H), 7.05 (s, 1H), 7.11-7.33 (m,
 5H).

4) Synthesis of N-[3-(1-(3-phenylpropan-1-yl)piperidin-4-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 0.8113 g (1.76 mM) of N-[3-(1-(3-phenylpropan-1-yl)piperidin-4-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (10 ml) was added 6 ml (24 mM) of 4N-HCl/methanol at room temperature and the mixture was stirred at room temperature for several minutes. The solvent was then distilled off under reduced pressure, and after addition of diethyl ether to the crystalline residue, the crystal crop was harvested by filtration and rinsed with ethanol and diethyl ether to provide the title compound.

Orange-colored crystals. Yield 821 mg (85%)

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.04-1.28 (m, 2H), 1.32-1.62 (m, 5H), 1.65-1.88 (m, 2H), 1.93-2.12 (m, 2H), 2.37-2.68 (m, 2H), 2.72-3.20 (m, 6H), 3.31-3.51 (m, 2H), 6.53 (d, J=7.2 Hz, 1H), 6.93 (d, J=8.8 Hz, 1H), 7.07 (s, 1H), 7.12-7.38 (m, 6H), 7.58 (s, 1H), 8.61-8.77 (m, 1H).

IR (KBr): 1635, 1562, 1529, 1446, 1300, 1217 cm⁻¹.

Elemental analysis for C²⁷H₃₄N₄O₂Cl₂•1.0H₂O

Calcd.: C, 58.79; H, 6.58; N, 10.16

Found : C, 58.66; H, 6.74; N, 10.12

Example 47

Synthesis of N-[3-(1-phenethylpiperidin-4-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) The procedure of Example 46-3) was generally followed to provide N-[3-(1-phenethylpiperidin-4-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

¹H-NMR (200 MHz, CDCl₃) δ: 1.21-2.16 (m, 11H), 2.57-2.66 (m, 2H), 2.81-2.89 (m, 2H), 2.92-3.12 (m, 2H), 3.24-3.34 (m, 2H), 5.66-5.77 (m, 1H), 5.80

(dd, J=1.7, 6.3 Hz, 1H), 6.58-6.73 (m, 3H), 7.06 (s, 1H), 7.14-7.37 (m, 5H).

2) The procedure of Example 46-4) was generally followed to provide N-[3-(1-phenethylpiperidin-4-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.
¹H-NMR (200 MHz, DMSO-d₆) δ: 1.94-2.21 (m, 2H), 2.66 (br t, J=7.7 Hz, 2H), 3.09-3.90 (m, 14H), 6.60 (d, J=7.4 Hz, 1H), 6.97 (d, J=9.0 Hz, 1H), 7.16-7.37 (m, 7H), 7.65 (s, 1H), 9.03-9.16 (m, 1H).
IR(KBr): 1639, 1564, 1535, 1500, 1446, 1292, 1217 cm⁻¹.
Elemental analysis for C₂₆H₃₂N₄OSCl₂•0.5H₂O

Calcd.: C, 59.08; H, 6.29; N, 10.60

Found : C, 59.03; H, 6.21; N, 10.52

15 Example 48

Synthesis of N-[3-(1-(3-(2-chlorophenyl)propan-1-yl)-piperidin-4-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[3-(1-(3-(2-chlorophenyl)propan-1-yl)piperidin-4-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a solution of 682.6 mg (4.0 mM) of 3-(2-chlorophenyl)propanol and 809.5 mg (8.0 mM) of triethylamine in ether (20 ml) was added 687.3 mg (6.0 mM) of methanesulfonyl chloride gradually with ice cooling and the mixture was stirred at that temperature for 5 minutes and further at room temperature for 30 minutes. To this reaction mixture was added 5% aqueous solution of sodium hydrogen carbonate and the reaction product was extracted into ethyl acetate. The organic layer was washed with water and dried over Na₂SO₄ and the solvent was distilled off under reduced pressure. To the resulting mesyl compound was added a solution of 830.8 mg (2.0 mM) of N-[3-(4-piperidyl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride and 1.15 g (10 mM) of triethylamine in

ethanol (10 ml) and the mixture was refluxed overnight. To this reaction mixture was added 5% aqueous solution of sodium hydrogen carbonate and the reaction product was extracted into ethyl acetate. The organic layer
5 was washed with water and dried over Na_2SO_4 and the solvent was then distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol = 3/1) to provide the title compound as reddish orange-colored
10 amorphous substance (580.0 mg, 58.6%).

$^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 1.10-1.40 (4H, m), 1.40-2.00 (9H, m), 2.38 (2H, t, $J=7.5$ Hz), 2.69 (2H, t, $J=7.8$ Hz), 2.93 (2H, br d, $J=11.0$ Hz), 3.22-3.32 (2H, m), 5.78 (1H, dd, $J=1.8$, 6.2 Hz), 5.80-5.90
15 (1H, m), 6.57-6.70 (3H, m), 7.03 (1H, s), 7.05-7.35 (4H, m).

IR (neat): 3307, 2927, 1618, 1556, 1477, 1443, 1281, 1151, 1055, 754 cm^{-1} .

2) Synthesis of N-[3-(1-(3-(2-chlorophenyl)propan-1-yl)piperidin-4-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 580.0 mg (1.2 mM) of N-[3-(1-(3-(2-chlorophenyl)propan-1-yl)piperidin-4-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in
25 ethanol (10 ml) was added 2 ml (8.0 mM) of 4N-HCl/ethyl acetate and the mixture was stirred for several minutes. The solvent was then distilled off under reduced pressure and ether was added to the residue. The resulting crystal crop was harvested by filtration and rinsed with ethanol and diethyl ether to provide the title compound as orange-colored crystals (605.4 mg, 91%).

$^1\text{H-NMR}$ (200 MHz, CD_3OD) δ : 1.25-1.80 (8H, m), 1.90-2.20 (4H, m), 2.75-3.05 (4H, m), 3.05-3.35 (3H, m), 3.54-3.60 (2H, m), 6.60 (1H, d, $J=7.4$ Hz), 6.92-7.00 (2H, m), 7.15-7.45 (5H, m), 7.50 (1H, s).

IR (KBr): 3464, 3215, 3049, 2939, 2656, 1635, 1568,
1539, 1502, 1473, 1437, 1298, 1219, 781, 756 cm⁻¹.

Elemental analysis for C₂₇H₃₃N₄OSCl₁•0.5H₂O

Calcd.: C, 56.20; H, 5.94; N, 9.71

5 Found : C, 56.29; H, 5.80; N, 9.61

Example 49

Synthesis of N-[3-(1-(2-chlorophenethyl)piperidin-4-yl)-propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

10 1) The procedure of Example 48-1) was generally followed to provide N-[3-(1-(2-chlorophenethyl)piperidin-4-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as deep-red solid.

15 ¹H-NMR (200 MHz, CDCl₃) δ: 1.10-1.40 (2H, m), 1.40-1.80 (4H, m), 1.90-2.30 (3H, m), 2.50-2.65 (2H, m), 2.80-3.15 (4H, m), 3.20-3.40 (2H, m), 3.43-3.54 (2H, m), 5.75-6.00 (2H, m), 6.55-6.80 (3H, m), 7.04 (1H, s), 7.05-7.40 (4H, m).

20 IR (KBr): 3390, 3265, 2927, 1740, 1697, 1643, 1618, 1558, 1514, 1481, 1371, 1286, 1153, 1119, 889, 771, 727, 675 cm⁻¹.

25 2) The procedure of Example 48-2) was generally followed to provide N-[3-(1-(2-chlorophenethyl)piperidin-4-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as light-orange-colored crystals.

30 ¹H-NMR (200 MHz, CD₃OD) δ: 1.25-1.70 (7H, m), 1.90-2.10 (2H, m), 2.95-3.40 (8H, m), 3.60-3.75 (2H, m), 6.60 (1H, d, J=7.8 Hz), 6.90 (1H, s), 6.98 (1H, d, J=9.2 Hz), 7.25-7.55 (6H, m).

IR (KBr): 3427, 3053, 2937, 2856, 2652, 1635, 1564, 1537, 1504, 1292, 1217, 771 cm⁻¹.

Elemental analysis for C₂₆H₃₁N₄OSCl₁•0.5H₂O

35 Calcd.: C, 55.47; H, 5.73; N, 9.95

Found : C, 55.72; H, 5.79; N, 9.96

Example 50

Synthesis of N-[3-(1-(1,4-benzodioxan-2-ylmethyl)-piperidin-4-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

5 1) The procedure of Example 48-1) was generally followed to provide N-[3-(1-(1,4-benzodioxan-2-ylmethyl)piperidin-4-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as reddish orange-colored amorphous substance.

10 $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 1.10-1.40 (4H, m), 1.40-1.80 (5H, m), 1.90-2.20 (2H, m), 2.49-2.71 (2H, m), 2.86-2.30 (2H, m), 3.23-3.33 (2H, m), 3.92-4.01 (1H, m), 4.20-4.40 (2H, m), 5.79 (1H, dd, $J=1.8, 6.0$ Hz), 5.80-5.95 (1H, m), 6.58-6.72 (3H, m), 6.75-6.98 (4H, m), 7.04 (1H, s).

15 IR (KBr): 3321, 2926, 1616, 1543, 1495, 1265, 1155, 1082, 1041, 750 cm^{-1} .

20 2) The procedure of Example 48-2) was generally followed to provide N-[3-(1-(1,4-benzodioxan-2-ylmethyl)piperidin-4-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

25 $^1\text{H-NMR}$ (200 MHz, CD_3OD) δ : 1.25-1.80 (7H, m), 1.85-2.10 (2H, m), 3.05-3.32 (5H, m), 3.35-3.40 (2H, m), 3.60-3.85 (2H, m), 4.03 (1H, dd, $J=6.3$ Hz, 11.3 Hz), 4.32 (1H, dd, $J=2.4, 11.6$ Hz), 6.61 (1H, d, $J=7.6$ Hz), 6.80-7.05 (6H, m), 7.34-7.43 (1H, m), 7.51 (1H, s).

30 IR (KBr): 3425, 3062, 2933, 1632, 1564, 1537, 1495, 1265, 758 cm^{-1} .

Elemental analysis for $\text{C}_{27}\text{H}_{32}\text{N}_4\text{O}_3\text{SCl}_2 \cdot 0.5\text{H}_2\text{O}$

Calcd.: C, 56.20; H, 5.94; N, 9.71

Found : C, 56.29; H, 5.80; N, 9.61

Example 51

35 Synthesis of N-methyl-N-[1-(3-phenylpropan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-

diazaacenaphthylene-4-carboxamide dihydrochloride

1) **Synthesis of N-methyl-N-(1-tert-butoxycarbonyl-piperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide**

5 To a solution of 0.58 g (1.84 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid N-hydroxysuccinimide ester, synthesized in the same manner as Example 42-1), in acetonitrile (6 ml) was added a solution of 0.50 g (2.19 mM) of tert-butyl 4-
10 [(methylamino)methyl]piperidine-1-carboxylic acid and 1.0 ml (7.2 mM) of triethylamine in acetonitrile (3 ml) at room temperature and the mixture was stirred at room temperature for 13 hours. The solvent was then distilled off under reduced pressure and the residue
15 was diluted with water and extracted with methylene chloride. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over MgSO₄, and purified by column chromatography (methanol/ethyl acetate 30%) to provide the title compound.

20 Red-purple solid. Yield 771 mg (98%)

¹H-NMR (200 MHz, CDCl₃) δ: 1.06-1.31 (m, 2H), 1.45 (s, 9H), 1.51-1.98 (m, 3H), 2.58-2.78 (m, 2H), 3.11 (br s, 3H), 3.21-3.40 (m, 2H), 4.01-4.22 (m, 2H), 5.74 (dd, J=1.8, 6.1 Hz, 1H), 6.06 (s, 1H), 6.55-
25 6.68 (m, 2H), 6.94 (s, 1H).

2) **Synthesis of N-methyl-N-(piperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride**

30 To a solution of 0.7716 g (1.8 mM) of N-methyl-N-(1-tert-butoxycarbonylpiperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (5 ml) was added 0.8 ml (9.6 mM) of 12N-hydrochloric acid at room temperature and the mixture was stirred for 18 hours. The solvent was then distilled off under reduced pressure, and 2 ml (24 mM) of 12N-hydrochloric acid was added to the residue. The mixture was stirred

for 5 minutes, after which ethanol was added and the solvent was distilled off under reduced pressure. To the residue was further added ethanol and the ethanol was distilled off under reduced pressure. The 5 resulting crystals were collected by filtration and rinsed serially with ethanol, acetone, and diethyl ether to provide the title compound.

Orange-colored solid. Yield 494.1 mg (68%)
¹H-NMR (200 MHz, D₂O) δ: 1.30-1.61 (m, 2H), 1.70-1.96
10 (m, 2H), 2.02-2.23 (m, 1H), 2.86-3.08 (m, 3H),
3.15-3.53 (m, 6H), 6.13 (d, J=7.4 Hz, 1H), 6.37
(s, 1H), 6.75 (d, J=9.2 Hz, 1H), 6.94 (dd, J=7.4
Hz, 9.2 Hz, 1H), 7.07 (s, 1H).

3) Synthesis of N-methyl-N-[1-(3-phenylpropan-1-yl)-
15 piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-
4-carboxamide

To a solution of 464.3 mg (1.16 mM) of N-methyl-N-(piperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride and 0.8 ml (5.74 mM) of triethylamine in ethanol was added 0.21 ml (1.38 mM) of 1-bromo-3-phenylpropane at room temperature, and the mixture was refluxed under nitrogen for 15 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted 25 with methylene chloride. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over MgSO₄, and purified by column chromatography (methanol/ethyl acetate 20-50%) to provide the title compound.

30 Red-purple solid. Yield 346 mg (67%)
¹H-NMR (200 MHz, CDCl₃) δ: 1.20-1.45 (m, 2H), 1.50-1.98
(m, 7H), 2.32-2.39 (m, 2H), 2.62 (t, J=7.7 Hz,
2H), 2.84-3.00 (m, 2H), 3.06 (br s, 3H), 3.35 (d,
J=7.0 Hz, 2H), 5.71 (dd, J=1.6, 6.4 Hz, 1H), 6.04
35 (s, 1H), 6.53-6.67 (m, 2H), 6.93 (s, 1H), 7.13-
7.32 (m, 5H).

4) Synthesis of N-methyl-N-[1-(3-phenylpropan-1-yl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 346.1 mg (0.77 mM) of N-methyl-N-[1-(3-phenylpropan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (4 ml) was added 2.0 ml (8.0 mM) of 4N-HCl/methanol and the mixture was stirred at room temperature for 20 minutes. The solvent was then distilled off under reduced pressure to provide the title compound.

Orange-colored amorphous solid. Yield 397 mg (90%)
¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40-2.18 (m, 7H), 2.63 (t, J=7.7 Hz, 2H), 2.73-3.55 (m, 11H), 6.65 (d, J=7.6 Hz, 1H), 6.60 (br s, 1H), 7.03 (d, J=9.2 Hz, 1H), 7.21-7.35 (m, 6H), 7.50 (s, 1H).

IR (KBr): 3417, 2935, 2721, 1628, 1498, 1448 cm⁻¹.

Elemental analysis for C₂₆H₃₂N₄OSCl₂•3.0H₂O

Calcd.: C, 54.44; H, 6.68; N, 9.77

Found : C, 54.32; H, 6.62; N, 9.64

20 Example 52

Synthesis of N-benzyl-N-[1-(3-phenylpropan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene dihydrochloride

1) Synthesis of N-benzyl-N-(1-tert-butoxycarbonyl-piperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene

To a solution of 1.26 g (4.0 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid N-hydroxysuccinimide ester, synthesized in the same manner as Example 42-1), in acetonitrile (12 ml) was added a solution of 1.40 g (4.79 mM) of tert-butyl 4-benzylaminomethyl)piperidine-1-carboxylic acid and 1.2 ml (8.6 mM) of triethylamine in acetonitrile (6 ml) at room temperature and the mixture was stirred at room temperature for 17 hours and further at 40°C for 3 days. The solvent was then distilled off under reduced pressure and the residue was diluted with water and

extracted with methylene chloride. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The attempt made to purify the residue by column chromatography

5 (methanol/ethyl acetate 20% methanol/chloroform = 1/15) failed. Thus, a crude product (0.5162 g) was obtained.

2) Synthesis of N-benzyl-N-(piperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene dihydrochloride

10 To a solution of crude N-benzyl-N-(1-tert-butoxy-carbonylpiperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene (0.5162 g) in ethanol (2 ml) was added 1.0 ml (12 mM) of 12N-hydrochloric acid and the mixture was stirred at room temperature for 15 hours. The solvent
15 was then distilled off under reduced pressure and the residue was diluted with water and washed with chloroform. Then, water was distilled off under reduced pressure to provide a crude product (0.451 g) as orange-colored solid.

20 3) Synthesis of N-benzyl-N-[1-(3-phenylpropan-1-yl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene

To a solution of crude N-benzyl-N-(piperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene dihydrochloride (0.451 g) and 0.7 ml (5.0 mM) of triethylamine in ethanol (4 ml) was added 0.17 ml (1.1 mM) of 1-bromo-3-phenylpropane at room temperature, and the mixture was refluxed under nitrogen for 15 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with methylene chloride. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The attempt to purify the residue by column chromatography (methanol/chloroform = 1/50-1/15, 1/20) failed. Thus, 35 the crude product was recovered as red-purple solid (245 mg).

¹H-NMR (200 MHz, CDCl₃) δ: 1.14-1.44 (m, 2H), 1.51-2.01
5 (m, 7H), 2.32-2.39 (m, 2H), 2.61 (t, J=7.7 Hz,
2H), 2.93 (br d, J=11.4 Hz, 2H), 3.25 (d, J=6.6
Hz, 2H), 4.69 (br s, 2H), 5.70 (dd, J=1.4, 6.4 Hz,
1H), 6.04 (s, 1H), 6.52-6.65 (m, 2H), 6.88 (s,
1H), 7.09-7.42 (m, 10H).

4) Synthesis of N-benzyl-N-[1-(3-phenylpropan-1-yl)-
piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene
dihydrochloride

10 To a solution of 245.4 mg (ca 0.47 mM) of crude N-
benzyl-N-[1-(3-phenylpropan-1-yl)piperidin-4-ylmethyl]-
5-thia-1,8b-diazaacenaphthylene in ethanol (4 ml) was
added 1.0 ml (4.0 mM) of 4N-HCl/methanol at room
temperature, and the mixture was stirred for 20

15 minutes. The solvent was then distilled off under
reduced pressure and diethyl ether was added to the
crystalline residue. The crystal crop was then
harvested by filtration to provide the title compound
as orange-colored solid.

20 Orange-colored crystals. Yield 174 mg (7%, 4 steps)
¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40-1.78 (m, 4H), 1.89-
2.13 (m, 3H), 2.63 (t, J=7.7 Hz, 2H), 2.71-3.53
(m, 8H), 4.66-4.87 (m, 2H), 6.64 (d, J=7.4 Hz,
1H), 6.69 (s, 1H), 7.02 (d, J=9.2 Hz, 1H), 7.16-
25 7.50 (m, 12H).

IR (KBr): 3425, 2937, 2667, 1630, 1498, 1439 cm⁻¹.
Elemental analysis for C₃₂H₃₆N₄OSCl₂•2.5H₂O
Calcd.: C, 59.99; H, 6.45; N, 8.75
Found : C, 60.26; H, 6.59; N, 8.53

30 Example 53
Synthesis of N-[2-(3-phenylpropan-1-ylamino)ethan-1-
yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
dihydrochloride
To a suspension of 1.09 g (ca 3.2 mM) of 5-thia-
35 1,8b-diazaacenaphthylene-4-carboxylic acid and 1.15 g
(10 mM) of N-hydroxysuccinimide in acetonitrile (15 ml)

was added 1.92 g (10 mM) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride at room temperature, and the mixture was stirred for 2 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄ and the solvent was distilled off under reduced pressure to provide a crude active ester (1.63 g). To a solution of this crude active ester (1.63 g) and 1.4 ml (10 mM) of triethylamine in acetonitrile (15 ml) was added 1.67 g (6.00 mM) of tert-butyl N-(2-aminoethan-1-yl)-3-phenylpropan-1-ylaminocarboxylate at room temperature, and the mixture was stirred at room temperature for 1 hour. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with methylene chloride. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The crude residue was subjected to column chromatography (methanol/ethyl acetate 10%), whereby a crude product (2.13 g, containing impurities) was obtained. To 413 mg (0.80 mM) of this crude product was added 1.5 ml (18 mM) of 12N-hydrochloric acid, and the mixture was stirred for several minutes. Then, ethanol and diethyl ether were added to the reaction mixture and the resulting crystals were collected by filtration and rinsed serially with ethanol, acetone, and diethyl ether to provide the title compound.

Orange-colored crystals. Yield 329 mg (91%)

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.84-2.03 (m, 2H), 2.67 (t, J=7.7 Hz, 2H), 2.84-3.09 (m, 4H), 3.39-3.51 (m, 2H), 6.60 (d, J=6.8 Hz, 1H), 6.96 (d, J=8.4 Hz, 1H), 7.16-7.37 (m, 7H), 7.65 (s, 1H), 9.00-

9.18 (m, 2H).

IR (KBr): 3431, 3236, 1636, 1568, 1502, 1292, 785 cm⁻¹.

Elemental analysis for C₂₁H₂₄N₄OSCl₂•0.1H₂O

Calcd.: C, 55.65; H, 5.38; N, 12.36

5 Found : C, 55.44; H, 5.19; N, 12.35

Example 54

The procedure of Example 53 was generally followed to provide N-[3-(3-phenylpropan-1-ylamino)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.73-2.01 (m, 4H), 2.67 (t, J=7.7 Hz, 2H), 2.81-2.97 (m, 4H), 3.15-3.26 (m, 2H), 6.61 (d, J=7.4 Hz, 1H), 6.97 (d, J=9.0 Hz, 1H), 7.20-7.33 (m, 7H), 7.65 (s, 1H), 8.95-9.15 (m, 1H).

IR (KBr): 3436, 2947, 2792, 1635, 1294 cm⁻¹.

Example 55

The procedure of Example 53 was generally followed to provide N-[4-(3-phenylpropan-1-ylamino)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.32-1.70 (m, 4H), 1.86-2.01 (m, 2H), 2.66 (t, J=7.7 Hz, 2H), 2.77-2.93 (m, 4H), 3.06-3.19 (m, 2H), 6.60 (d, J=6.8 Hz, 1H), 6.97 (d, J=8.4 Hz, 1H), 7.15-7.34 (m, 7H), 7.64 (s, 1H), 8.82-9.10 (m, 1H).

IR (KBr): 3411, 2944, 2786, 1637, 1565, 1292 cm⁻¹.

Elemental analysis for C₂₃H₂₈N₄OSCl₂

Calcd.: C, 57.62; H, 5.89; N, 11.69

30 Found : C, 57.32; H, 5.91; N, 11.57

Example 56

Synthesis of N-[3-(N-methyl-N-(3-phenylpropan-1-yl)amino)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

35 1) Synthesis of N-[3-(N-methyl-N-(3-phenylpropan-1-yl)-amino)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-

carboxamide

To a solution of 0.50 g (1.59 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid N-hydroxysuccinimide ester, synthesized in the same manner as Example 42-1), in acetonitrile (6 ml) was added a solution of 0.39 g (1.89 mM) of [3-(N-methyl-N-(3-phenylpropan-1-yl)amino)propan-1-yl]amine and 0.5 ml (3.59 mM) of triethylamine in acetonitrile (4 ml) at room temperature, and the mixture was stirred for 5 minutes. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with methylene chloride. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over MgSO₄, and purified by column chromatography (methanol/ethyl acetate 80-100%) to provide the title compound.

Red-purple oil. Yield 577 mg (89%)

¹H-NMR (200 MHz, CDCl₃) δ: 1.57-1.73 (m, 2H), 1.77-1.95 (m, 2H), 2.25 (s, 3H), 2.40-2.55 (m, 4H), 2.66 (t, J=7.7 Hz, 2H), 3.37-3.45 (m, 2H), 5.58 (d, J=6.4 Hz, 1H), 6.49-6.64 (m, 3H), 6.89 (s, 1H), 7.12-7.3 (m, 5H), 8.37-8.60 (m, 1H).

2) Synthesis of N-[3-(N-methyl-N-(3-phenylpropan-1-yl)-amino)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 577.3 mg (1.42 mM) of N-[3-(N-(3-phenylpropan-1-yl)amino)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (6 ml) was added 2.0 ml (8.0 mM) of 4N-HCl/methanol at room temperature and the mixture was stirred for several minutes. The solvent was then distilled off under reduced pressure to provide the title compound.

Orange-colored amorphous substance. Yield 670 mg (87%)
¹H-NMR (200 MHz, DMSO-d₆) δ: 1.71-2.07 (m, 4H), 2.60-2.73 (m, 5H), 2.89-3.25 (m, 6H), 6.62 (d, J=7.4 Hz, 1H), 6.98 (d, J=9.2 Hz, 1H), 7.16-7.36 (m,

7H), 7.66 (s, 1H), 8.92-9.03 (m, 1H).

IR (KBr): 3433, 3059, 2951, 2715, 1637, 1296 cm⁻¹.

Elemental analysis for C₂₃H₂₈N₄O₂SCl₂•2.5H₂O

Calcd.: C, 52.67; H, 6.34; N, 10.68

5 Found : C, 52.40; H, 6.25; N, 10.39

Example 57

Synthesis of 4-[4-(3-phenylpropan-1-yl)piperazino-1-carbonyl]-5-thia-1,8b-diazaacenaphthylene dihydrochloride

10 1) Synthesis of 4-(4-tert-butoxycarbonylpiperazino-1-carbonyl)-5-thia-1,8b-diazaacenaphthylene

To a solution of 0.85 g (2.7 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid N-

15 hydroxysuccinimide ester, synthesized in the same manner as Example 42-1), in acetonitrile (10 ml) was added a suspension of 0.28 g (3.25 mM) of piperazine and 0.75 ml (5.38 mM) of triethylamine in acetonitrile (3 ml) at room temperature, and the mixture was stirred at room temperature for 30 minutes. To this reaction

20 mixture was added 1.0 ml (4.3 mM) of di-tert-butyl dicarbonate, and the mixture was stirred at room temperature for 2.5 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with methylene

25 chloride. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The attempt to purify the residue by column chromatography (methanol/ethyl acetate 10%) failed. As a consequence, a crude product was recovered as red-purple amorphous substance.

¹H-NMR (200 MHz, CDCl₃) δ: 1.48 (s, 9H), 3.25-3.73 (m, 8H), 5.74 (dd, J=1.8, 5.8 Hz, 1H), 6.12 (s, 1H), 6.56-6.67 (m, 2H), 6.95 (s, 1H).

2) Synthesis of 4-(piperazino-1-carbonyl)-5-thia-1,8b-diazaacenaphthylene dihydrochloride

To a solution of 0.5092 g (ca 1.3 mM) of crude 4-

(4-tert-butoxycarbonylpiperazino-1-carbonyl)-5-thia-1,8b-diazaacenaphthylene in ethanol (4 ml) was added 0.54 ml (6.48 mM) of 12N-hydrochloric acid at room temperature, and the mixture was stirred for 15 hours.

5 The resulting crystals were filtered off and the filtrate was concentrated to provide a crude product as orange-colored solid (333 mg).

¹H-NMR (200 MHz, D₂O) δ: 3.20-3.48 (m, 4H), 3.90-4.03 (m, 4H), 6.17 (d, J=7.0 Hz, 1H), 6.43 (s, 1H), 10 6.78 (d, J=9.4 Hz, 1H), 6.94-7.02 (m, 1H), 7.11 (s, 1H).

3) Synthesis of 4-[4-(3-phenylpropan-1-yl)piperazino-1-carbonyl]-5-thia-1,8b-diazaacenaphthylene

To a solution of 333 mg (ca 0.927 mM) of 4-(piperazino-1-carbonyl)-5-thia-1,8b-diazaacenaphthylene dihydrochloride and 0.65 ml (4.66 mM) of triethylamine in ethanol (6 ml) was added 0.17 ml (1.1 mM) of 1-bromo-3-phenylpropane at room temperature and the mixture was refluxed under nitrogen for 48 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with methylene chloride. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over MgSO₄, and purified by column chromatography (methanol/ethyl acetate 20-40%) to provide the title compound.

Red-purple amorphous substance. Yield 160 mg (15%, 3 steps)

¹H-NMR (200 MHz, CDCl₃) δ: 1.78-1.90 (m, 2H), 2.40-2.47 (m, 6H), 2.65 (t, J=7.7 Hz, 2H), 3.63-3.68 (m, 4H), 5.71 (dd, J=1.6, 6.2 Hz, 1H), 6.01 (s, 1H), 6.53-6.66 (m, 2H), 6.93 (s, 1H), 7.15-7.34 (m, 5H).

IR (KBr): 3425, 2595, 1632, 1498, 1431, 1273, 1211, 966 35 cm⁻¹.

4) Synthesis of 4-[4-(3-phenylpropan-1-yl)piperazino-1-

carbonyl]-5-thia-1,8b-diazaacenaphthylene
dihydrochloride

To a solution of 160 mg (0.40 mM) of 4-[4-(3-phenylpropan-1-yl)piperazino-1-carbonyl]-5-thia-1,8b-diazaacenaphthylene in ethanol (2 ml) was added 0.5 ml (2.0 mM) of 4N-HCl/methanol. The solvent was then distilled off under reduced pressure to provide the title compound.

Orange-colored amorphous substance. Yield 183 mg (90%)
10 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.96-2.13 (m, 2H), 2.65

(t, J=7.8 Hz, 2H), 2.94-3.16 (m, 4H), 3.42-3.63
(m, 4H), 4.20-4.36 (m, 2H), 6.65 (d, J=8.6 Hz,
1H), 6.67 (s, 1H), 7.03 (d, J=9.2 Hz, 1H), 7.17-
7.36 (m, 6H), 7.52 (s, 1H).

15 IR (KBr): 3439, 3060, 2942, 1637, 1329, 1120, 791 cm⁻¹.
Elemental analysis for C₂₃H₂₆N₄OSCl₂•1.5H₂O

Calcd.: C, 54.76; H, 5.79; N, 11.11

Found : C, 54.72; H, 6.03; N, 10.87

Example 58

20 Synthesis of N-[2-(4-(3-phenylpropan-1-yl)piperazin-1-yl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride

1) Synthesis of N-[2-(4-tert-butoxycarbonyl-1-piperazinyl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

In 50 ml of acetonitrile were suspended 3.27 g (15.0 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 3.45 g (30.0 mM) of N-hydroxysuccinimide, followed by addition of 5.75 g (30.0 mM) of N-ethyl-N'-3-(N,N-di-methylamino)propylcarbodiimide hydrochloride, and the mixture was stirred at room temperature for 1 hour. The solvent was then distilled off under reduced pressure and the residue was extracted with chloroform (150 ml). The organic layer was washed with 100 ml of saturated aqueous solution of sodium chloride and dried

over MgSO₄ and the solvent was distilled off under reduced pressure to provide the active ester. To a solution of this active ester in 100 ml of chloroform were added 4.2 ml (30.0 mM) of triethylamine and 1.94 g (15.0 mM) of 1-(2-aminoethyl)piperazine and the mixture was stirred at room temperature for 30 minutes. Then, 3.28 g (15.0 mM) of di-tert-butyl dicarbonate was added dropwise and the mixture was further stirred at room temperature for 1 hour. This reaction mixture was washed with 100 ml of purified water and the organic layer was further washed with 150 ml of saturated aqueous solution of sodium chloride. The organic layer was dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol = 10/1) to provide the title compound. Yield 3.64 g (56.5%, red liquid).

¹H-NMR (200 MHz, CDCl₃) δ: 1.47 (s, 9H), 2.42 (m, 4H), 2.53 (t, 2H, J=6.0 Hz), 3.35-3.48 (m, 6H), 5.80 (dd, 1H, J=6.2, 4.4 Hz), 6.42 (br s, 1H, NH), 6.62-6.70 (m, 3H), 7.05 (s, 1H).

IR (KBr): 1687, 1622, 1280, 1161 cm⁻¹.

2) Synthesis of N-[2-(piperazinyl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride
To a solution of 3.60 g (8.38 mM) of N-[2-(4-tert-butoxycarbonyl-1-piperazinyl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in 100 ml of ethanol was added 3.4 ml (41.90 mM) of 12N-hydrochloric acid and the mixture was stirred at room temperature for one hour. The resulting crystals were collected by filtration and rinsed with small amounts of ethanol and ether to provide the title compound. Yield 3.36 g (91.4%, orange-colored crystals).

¹H-NMR (200 MHz, DMSO-d₆) δ: 3.30-3.59 (m, 12H), 6.64 (d, 1H, J=7.0 Hz), 7.01 (d, 1H, J=8.2 Hz), 7.28-7.36 (m, 2H), 7.69 (s, 1H), 9.18 (t, 1H, NH, J=5.6

Hz), 9.90 (br s, 2H, NH).
IR (KBr): 1641, 1568, 1298 cm⁻¹.

3) Synthesis of N-[2-(4-(3-phenylpropan-1-yl)piperazin-1-yl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a solution of 1.63 g (3.71 mM) of N-[2-(1-piperazinyl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride and 3.0 ml (21.5 mM) of triethylamine in ethanol (16 ml) was added 0.68 ml (4.47 mM) of 1-bromo-3-phenylpropane at room temperature, and the mixture was refluxed under nitrogen for 20 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over MgSO₄, and purified by column chromatography (methanol/ethyl acetate 20-50%) to provide the title compound.

Red-purple amorphous substance. Yield 1.15 g (69%).
¹H-NMR (200 MHz, CDCl₃) δ: 1.73-1.93 (m, 2H), 2.36-2.68 (m, 14H), 3.33-3.42 (m, 2H), 5.78 (dd, J=1.8, 6.2 Hz, 1H), 6.46-6.66 (m, 4H), 7.04 (s, 1H), 7.15-7.31 (m, 5H).

4) Synthesis of N-[2-(4-(3-phenylpropan-1-yl)piperazin-1-yl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride

To a solution of 1.15 g (2.57 mM) of N-[2-(4-(3-phenylpropan-1-yl)piperazin-1-yl)ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (10 ml) was added 4 ml (16 mM) of 4N-HCl/methanol at room temperature and the mixture was stirred at room temperature for several minutes. The solvent was then distilled off under reduced pressure and diethyl ether was added to the residue. The resulting crystals were collected by filtration and rinsed with ethanol and diethyl ether to provide the title compound.

Orange-colored crystals. Yield 1.27 g (85%)

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.94-2.21 (m, 2H), 2.66
(br t, J=7.7 Hz, 2H), 3.09-3.90 (m, 14H), 6.60 (d,
J=7.4 Hz, 1H), 6.97 (d, J=9.0 Hz, 1H), 7.16-7.37
5 (m, 7H), 7.65 (s, 1H), 9.03-9.16 (m, 1H).

IR (KBr): 1641, 1560, 1535, 1497, 1443, 1288, 1215,
1107, 958, 794 cm⁻¹.

Elemental analysis for C₂₅H₃₂N₅OSCl₃•1.5H₂O

Calcd.: C, 51.42; H, 6.04; N, 11.99

10 Found : C, 51.51; H, 5.79; N, 11.81

Example 59

Synthesis of N-[3-(4-(3-phenylpropan-1-yl)piperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride

15 1) The procedure of Example 58-1) was generally followed to provide N-[3-(4-tert-butoxycarbonyl-1-piperazinyl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red oil.

¹H-NMR (200 MHz, CDCl₃) δ: 1.47 (s, 9H), 1.62-1.80 (m, 2H), 2.33-2.59 (m, 6H), 3.35-3.48 (m, 2H), 3.48-3.59 (m, 4H), 5.74 (dd, J=1.4, 6.4 Hz, 1H), 6.57-6.71 (m, 3H), 7.02 (s, 1H), 7.70 (t, J=5.4 Hz, 1H).

IR (KBr): 3327, 1695, 1626 cm⁻¹.

20 2) The procedure of Example 58-2) was generally followed to provide N-[3-(1-piperazinyl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride as orange-colored crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.83-2.05 (m, 2H), 3.04-3.32 (m, 6H), 3.32-3.77 (m, 6H), 6.68 (d, J=7.2 Hz, 1H), 7.03 (d, J=8.8 Hz, 1H), 7.27 (s, 1H), 7.35 (dd, J=7.2, 8.8 Hz, 1H), 7.73 (s, 1H), 9.06 (t, J=5.6 Hz, 1H), 9.94 (br s, 2H).

IR (KBr): 3363, 1639, 1556 cm⁻¹.

35 3) The procedure of Example 58-3) was generally followed to provide N-[3-(4-(3-phenylpropan-1-

yl)piperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red oil.

¹H-NMR (200 MHz, CDCl₃) δ: 1.51-1.92 (m, 4H), 2.29-2.71 (m, 14H), 3.37-3.45 (m, 2H), 5.69 (dd, J=1.2, 6.4 Hz, 1H), 6.51-6.66 (m, 3H), 6.98 (s, 1H), 7.12-7.35 (m, 5H), 8.07-8.24 (m, 1H).

IR (KBr): 3255, 2939, 2814, 1620, 1545, 1279, 1151 cm⁻¹.

4) The procedure of Example 58-4) was generally followed to provide N-[3-(4-(3-phenylpropan-1-yl)piperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride as orange-colored crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.78-2.10 (m, 4H), 2.56-2.72 (m, 2H), 2.98-4.09 (m, 14H), 6.51 (d, J=7.4 Hz, 1H), 6.91 (d, J=9.2 Hz, 1H), 7.04-7.38 (m, 7H), 7.57 (s, 1H), 8.76-8.89 (m, 1H). IR (KBr): 3174, 3035, 2366, 1630, 1441, 1296, 1211, 795 cm⁻¹.

Elemental analysis for C₂₆H₃₄N₅OSCl₃•0.5H₂O

Calcd.: C, 53.84; H, 6.08; N, 12.07
Found.: C, 53.84; H, 5.80; N, 12.29

Example 60

Synthesis of N-[1-(3-phenylpropan-1-yl)pyrrolidin-3-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[3-(1-tert-butoxycarbonyl)pyrrolidinyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

In 50 ml of acetonitrile were suspended 3.27 g (15.0 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 3.45 g (30.0 mM) of N-hydroxysuccinimide, followed by addition of 5.75 g (30.0 mM) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride, and the mixture was stirred at room temperature for 1 hour. The solvent was then distilled off under reduced

pressure and the residue was extracted with 150 ml of chloroform. The organic layer was washed with 100 ml of saturated aqueous solution of sodium chloride and dried over $MgSO_4$ and the solvent was distilled off under reduced pressure to provide the active ester. To a solution of this active ester in 100 ml of chloroform were added 4.2 ml (30.0 mM) of triethylamine and 1.55 g (15.0 mM) of 3-aminopyrrolidine, and the mixture was stirred at room temperature for 30 minutes. Then, 3.28 g (15.0 mM) of di-tert-butyl dicarbonate was added dropwise and the mixture was further stirred at room temperature for 1 hour. This reaction mixture was then washed by adding 100 ml of purified water and the organic layer was further washed with 150 ml of saturated aqueous solution of sodium chloride. The organic layer was dried over $MgSO_4$ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol = 10/1) to provide the title compound. Yield 3.22 g (55.5%, red solid).

1H -NMR (200 MHz, $CDCl_3$) δ : 1.46 (s, 9H), 1.81-2.02 (m, 1H), 2.08-2.28 (m, 1H), 3.43-3.88 (m, 4H), 4.12-4.27 (m, 1H), 4.74 (d, 1H, NH, $J=6.0$ Hz), 5.73 (dd, 1H, $J=5.6$, 3.2 Hz), 6.23 (s, 1H), 6.58-6.66 (m, 2H), 6.95 (s, 1H).
IR (KBr): 1697, 1608, 1163 cm^{-1} .

2) Synthesis of N-(3-pyrrolidinyl)-5-thia-1,8b-diaza-acenaphthylene-4-carboxamide dihydrochloride

To a solution of 3.2 g (8.28 mM) of N-[3-(1-tert-butoxycarbonyl)pyrrolidinyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in 100 ml of ethanol was added 3.4 ml (41.40 mM) of 12N-hydrochloric acid and the mixture was stirred at room temperature for 1 hour. The resulting crystals were collected by filtration and rinsed with small amounts of ethanol and ether to provide the title compound. Yield 2.12 g

(89.4%, orange-colored crystals).

¹H-NMR (200 MHz, DMSO-d₆) δ: 2.04-2.32 (m, 2H), 3.61-3.84 (m, 5H), 6.65 (d, 1H, J=7.4 Hz), 6.87 (s, 1H), 7.04 (d, 1H, J=9.2 Hz), 7.32 (t, 1H, J=7.6 Hz), 7.59 (s, 1H), 8.51 (br s, 2H, NH).
IR (KBr): 1605, 1497, 1427 cm⁻¹.

3) Synthesis of N-[1-(3-phenylpropan-1-yl)pyrrolidin-3-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a solution of 0.50 g (1.39 mM) of N-(3-pyrrolidinyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride and 1.0 ml (7.17 mM) of triethylamine in ethanol (5 ml) was added 0.25 ml (1.64 mM) of 1-bromo-3-phenylpropane at room temperature, and the mixture was refluxed under nitrogen for 18 hours. To this reaction mixture was further added 0.2 ml (1.32 mM) of 1-bromo-3-phenylpropane, and the mixture was further refluxed for 3 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with chloroform.

The organic layer was washed with saturated aqueous solution of sodium chloride, dried over MgSO₄, and purified by column chromatography (methanol/ethyl acetate 20-30%) to provide N-[1-(3-phenylpropan-1-yl)pyrrolidin-3-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide.

Red-purple amorphous substance. Yield 242 mg (43%).

¹H-NMR (200 MHz, CDCl₃) δ: 1.67-2.20 (m, 4H), 2.61-2.71 (m, 4H), 3.24-3.41 (m, 2H), 3.49-3.83 (m, 3H), 5.71 (dd, J=2.2, 5.8 Hz, 1H), 6.22 (s, 1H), 6.51-6.62 (m, 2H), 6.93 (s, 1H), 7.16-7.32 (m, 6H).

4) Synthesis of N-[1-(3-phenylpropan-1-yl)pyrrolidin-3-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 242.4 mg (0.60 mM) of N-[1-(3-phenylpropan-1-yl)pyrrolidin-3-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (2 ml) was

added 1.5 ml (6.0 mM) of 4N-HCl/methanol at room temperature and the mixture was stirred at room temperature for several minutes. The solvent was then distilled off under reduced pressure and diethyl ether was added to the residue. The resulting crystals were collected by filtration and rinsed with diethyl ether to provide the title compound.

5 Orange-colored crystals. Yield 253 mg (88%)
¹H-NMR (200 MHz, DMSO-d₆) δ: 1.88-2.09 (m, 2H), 2.14-
10 2.31 (m, 2H), 2.69 (t, J=7.6 Hz, 2H), 2.88-3.03
(m, 2H), 3.46-4.07 (m, 5H), 6.62 (d, J=7.4 Hz,
1H), 6.86 (s, 1H), 7.09 (d, J=9.2 Hz, 1H), 7.15-
7.37 (m, 6H), 7.55 (s, 1H), 9.41-9.82 (m, 1H).
IR (KBr): 1624, 1498, 1437, 1390, 1211, 785 cm⁻¹.

15 Example 61

Synthesis of N-[(3R)-1-(3-phenylpropan-1-yl)pyrrolidin-3-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) The procedure of Example 60-1) was generally followed to provide N-[(3R)-1-tert-butoxycarbonylpyrrolidinyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red solid.
¹H-NMR (200 MHz, CDCl₃) δ: 1.46 (s, 9H), 1.78-1.98 (m, 1H), 2.04-2.28 (m, 1H), 3.36-3.92 (m, 4H), 4.12-
20 4.30 (m, 1H), 4.56-4.72 (m, 1H), 5.72 (dd, J=2.2, 5.6 Hz, 1H), 6.23 (s, 1H), 6.58-6.71 (m, 2H), 6.95
(s, 1H).
IR (KBr): 1697, 1608, 1163 cm⁻¹.

2) The procedure of Example 60-2) was generally followed to provide N-[(3R)-pyrrolidinyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.
¹H-NMR (200 MHz, DMSO-d₆) δ: 2.07-2.29 (m, 1H), 2.34-
25 2.55 (m, 1H), 3.39-4.16 (m, 5H), 6.08 (d, J=7.3 Hz, 1H), 6.53 (s, 1H), 6.70 (d, J=8.9 Hz, 1H),
30 6.89 (dd, 7.3, 8.9 Hz, 1H), 7.08 (s, 1H).

IR (KBr): 1603, 1500, 1433 cm⁻¹.

3) The procedure of Example 60-3) was generally followed to provide N-[(3R)-1-(3-phenylpropan-1-yl)pyrrolidin-3-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

5 ¹H-NMR (200 MHz, CDCl₃) δ: 1.67-2.20 (m, 4H), 2.61-2.71 (m, 4H), 3.24-3.41 (m, 2H), 3.49-3.83 (m, 3H), 5.71 (dd, J=2.2, 5.6 Hz, 1H), 6.22 (s, 1H), 6.51-6.62 (m, 2H), 6.93 (s, 1H), 7.16-7.32 (m, 6H).

10 4) The procedure of Example 60-4) was generally followed to provide N-[(3R)-1-(3-phenylpropan-1-yl)pyrrolidin-3-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

15 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.87-2.07 (m, 2H), 2.12-2.33 (m, 2H), 2.69 (t, J=7.6 Hz, 2H), 2.88-3.04 (m, 2H), 3.46-4.07 (m, 5H), 6.58 (d, J=7.2 Hz, 1H), 6.83 (s, 1H), 6.98 (d, J=9.2 Hz, 1H), 7.16-7.38 (m, 6H), 7.51 (s, 1H), 9.31-9.70 (m, 1H).

IR (KBr): 1624, 1498, 1437, 1390, 1211, 785 cm⁻¹.

20 Elemental analysis for C₂₃H₂₆N₄OSCl₂•1.6H₂O

Calcd.: C, 54.56; H, 5.81; N, 11.07

Found : C, 54.44; H, 6.09; N, 11.04

Example 62

25 Synthesis of N-[(3S)-1-(3-phenylpropan-1-yl)pyrrolidin-3-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

30 1) The procedure of Example 60-1) was generally followed to provide N-[(3s)-(1-tert-butoxycarbonyl)pyrrolidinyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red solid.

35 ¹H-NMR (200 MHz, CDCl₃) δ: 1.46 (s, 9H), 1.78-1.91 (m, 1H), 2.04-2.28 (m, 1H), 3.36-3.92 (m, 4H), 4.12-4.30 (m, 1H), 4.56-4.72 (m, 1H), 5.72 (dd, J=2.2, 5.6 Hz, 1H), 6.23 (s, 1H), 6.53-6.71 (m, 2H), 6.95 (s, 1H).

IR (KBr): 1697, 1608, 1163 cm⁻¹.

2) The procedure of Example 60-2) was generally followed to provide N-[(3s)-pyrrolidinyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

5 $^1\text{H-NMR}$ (200 MHz, DMSO-d₆) δ : 2.07-2.29 (m, 1H), 2.34-2.55 (m, 1H), 3.39-4.16 (m, 5H), 6.08 (d, J=7.3 Hz, 1H), 6.53 (s, 1H), 6.70 (d, J=8.9 Hz, 1H), 6.89 (dd, 7.3, 8.9 Hz, 1H), 7.08 (s, 1H).
IR (KBr): 1606, 1496, 1425 cm⁻¹.

10 3) The procedure of Example 60-3) was generally followed to provide N-[(3S)-1-(3-phenylpropan-1-yl)pyrrolidin-3-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

15 $^1\text{H-NMR}$ (200 MHz, CDCl₃) δ : 1.67-2.20 (m, 4H), 2.61-2.71 (m, 4H), 3.24-3.41 (m, 2H), 3.49-3.83 (m, 3H), 5.71 (dd, J=2.2, 5.6 Hz, 1H), 6.22 (s, 1H), 6.51-6.62 (m, 2H), 6.93 (s, 1H), 7.16-7.32 (m, 6H).

20 4) The procedure of Example 60-4) was generally followed to provide N-[(3S)-1-(3-phenylpropan-1-yl)pyrrolidin-3-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

25 $^1\text{H-NMR}$ (200 MHz, DMSO-d₆) δ : 1.88-2.08 (m, 2H), 2.14-2.33 (m, 2H), 2.68 (t, J=7.6 Hz, 2H), 2.88-3.05 (m, 2H), 3.28-4.32 (m, 5H), 6.56 (d, J=7.0 Hz, 1H), 6.82 (s, 1H), 6.96 (d, J=9.2 Hz, 1H), 7.16-7.37 (m, 6H), 7.50 (s, 1H), 9.22-9.63 (m, 1H).
IR (KBr): 1624, 1498, 1437, 1390, 1211, 785 cm⁻¹.

Elemental analysis for C₂₃H₂₆N₄O₂SCl₂•1.5H₂O
Calcd.: C, 54.76; H, 5.79; N, 11.11
30 Found : C, 54.46; H, 5.83; N, 11.01

Example 63

Synthesis of 4-[4-(3-phenylpropan-1-ylaminomethyl)-piperidino-1-carbonyl]-5-thia-1,8b-diazaacenaphthylene dihydrochloride

35 1) Synthesis of 4-[4-(3-phenylpropan-1-ylaminomethyl)-piperidino-1-carbonyl]-5-thia-1,8b-diazaacenaphthylene

To a solution of 0.21 g (0.67 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid N-hydroxysuccinimide ester, synthesized in the same manner as Example 42-1), in acetonitrile (2 ml) was added a solution of 0.1858 g (0.8 mM) of 4-[(3-phenylpropan-1-yl)aminomethyl]piperidine and 0.15 ml (1.08 mM) of triethylamine in acetonitrile (2 ml) at 0°C and the mixture was stirred at the prevailing temperature for 4 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over MgSO₄, and purified by column chromatography (methanol/ethyl acetate 20-50-100%) to provide the title compound.

Red-purple amorphous substance. Yield 180 mg (62%)
¹H-NMR (200 MHz, CDCl₃) δ: 1.02-1.30 (m, 2H), 1.57-1.91 (m, 5H), 2.50 (d, J=6.2 Hz, 2H), 2.59-2.70 (m, 4H), 2.81-2.93 (m, 2H), 4.30-4.37 (m, 2H), 5.71 (dd, J=1.6, 6.2 Hz, 1H), 6.05 (s, 1H), 6.53-6.66 (m, 2H), 6.92 (s, 1H), 7.15-7.32 (m, 5H).

2) Synthesis of 4-[4-(3-phenylpropan-1-ylaminomethyl)-piperidino-1-carbonyl]-5-thia-1,8b-diazaacenaphthylene dihydrochloride

To a solution of 180.9 mg (0.42 mM) of 4-[4-(3-phenylpropan-1-ylaminomethyl)piperidino-1-carbonyl]-5-thia-1,8b-diazaacenaphthylene in ethanol (2 ml) was added 1.0 ml (4 mM) of 4N-HCl/methanol at room temperature and the mixture was stirred for several minutes. The solvent was then distilled off under reduced pressure to provide the title compound.

Orange-colored amorphous substance. Yield 201 mg (86%)
¹H-NMR (200 MHz, DMSO-d₆) δ: 1.09-1.28 (m, 2H), 1.77-2.08 (m, 5H), 2.58-3.04 (m, 8H), 4.06-4.24 (m, 2H), 6.52 (s, 1H), 6.65 (d, J=7.2 Hz, 1H), 7.03 (d, J=9.2 Hz, 1H), 7.15-7.37 (m, 6H), 7.50 (s,

1H), 8.93-9.19 (m, 1H).

IR (KBr): 3421, 2945, 2794, 1628, 1500, 1444, 1387,
1281, 1215 cm⁻¹.

Elemental analysis for C₂₅H₃₀N₄OSCl₂•3.0H₂O

5 Calcd.: C, 53.66; H, 6.48; N, 10.01
Found : C, 53.88; H, 6.59; N, 10.04

Example 64

Synthesis of N-[3-(4-benzyl-1,4-diazepin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide tri-
10 hydrochloride

1) Synthesis of N-[3-(1-tert-butoxycarbonyl-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

In acetonitrile (50 ml) was suspended 2619 mg (12 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 2762 mg (24 mM) of N-hydroxysuccinimide, followed by addition of 4601 mg (24 mM) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride, and the mixture was stirred at room temperature for 1 hour. The solvent was then distilled off under reduced pressure and the residue was extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The solvent was then distilled off under reduced pressure to provide the active ester. To a solution of this active ester in chloroform (100 ml) were added 4.2 ml (30 mM) of triethylamine and 3710 mg (14 mM) of 1-tert-butoxycarbonyl-4-(3-aminopropyl)-2,3,5,6-hexahydro-7H-1,4-diazepine, and the mixture was stirred at room temperature for 30 minutes. This reaction mixture was washed with purified water and the organic layer was further washed with saturated aqueous solution of sodium chloride. The organic layer was dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by column chromatography (ethyl acetate/ethanol = 10/1) to provide the

title compound as red solid. Yield 4291 mg (78.2%).

¹H-NMR (200 MHz, CDCl₃) δ: 1.47 (s, 9H), 1.62-1.83 (m, 2H), 1.83-2.16 (m, 2H), 2.51-2.83 (m, 6H), 3.29-3.55 (m, 6H), 5.71 (dd, 1H, J=5.8, 2.2 Hz), 6.54-6.77 (m, 3H), 7.03 (d, 1H, J=4.0 Hz), 7.76 (d, 1H, J=14.8 Hz).

2) Synthesis of N-[3-(hexahydro-1,4-diazepin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride

To a solution of 4250 mg (9.29 mM) of N-[3-(4-tert-butoxycarbonyl-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in 100 ml of ethanol was added 3.8 ml (46.44 mM) of 12N-hydrochloric acid, and the mixture was stirred at room temperature for 1 hour. The resulting precipitate was recovered by filtration and rinsed with small amounts of ethanol and ether to provide the title compound. Yield 4020 mg (92.8%).

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.82-2.06 (m, 2H), 2.09-2.31 (m, 2H), 3.02-3.42 (m, 6H), 3.46-3.82 (m, 6H), 6.65 (d, 1H, J=7.4 Hz), 7.02 (d, 1H, J=9.2 Hz), 7.28 (s, 1H), 7.32 (dd, 1H, J=9.2, 7.4 Hz), 7.70 (s, 1H), 9.07 (t, 1H, J=5.6 Hz).

3) Synthesis of N-[3-(4-benzyl-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

In 10 ml of ethanol were suspended 606.9 mg (1.3 mM) of N-[3-(hexahydro-1,4-diazepin-1-yl)propan-1-yl]-5-thia-1,8-diazaacenaphthylene-4-carboxamide trihydrochloride and 342.1 mg (2.0 mM) of benzyl bromide, followed by addition of 0.91 ml (6.5 mM) of triethylamine, and the mixture was refluxed overnight. This reaction mixture was diluted with 5% aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride and dried

over Na_2SO_4 . The solvent was then distilled off under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate/methanol = 2/3) to provide the title compound as deep-red liquid
5 (320.0 mg, 55.0%).

10 $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 1.60-1.75 (2H, m), 1.75-1.95 (2H, m), 2.60-2.85 (10H, m), 3.37-3.45 (2H, m), 3.63 (2H, s), 5.71 (1H, dd, $J=1.7, 6.1$ Hz), 6.54-6.66 (3H, m), 6.96 (1H, s), 7.20-7.35 (5H, m), 8.40 (1H, br s).
10 IR (neat): 3286, 3059, 2933, 2818, 1618, 1547, 1508, 1481, 1452, 1348, 1281, 1213, 1155, 1120, 773, 733, 700, 650 cm^{-1} .

15 4) Synthesis of N-[3-(4-benzyl-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride
20 To a solution of 320.0 mg (0.71 mM) of N-[3-(4-benzyl-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (10 ml) was added 2 ml (8.0 mM) of 4N-HCl/ethyl acetate, and the mixture was stirred under heating for 2 hours. To the ethanolic solution containing crystals was added ether and the crystal crop was harvested by filtration and rinsed with ethanol and diethyl ether to 25 provide the title compound as light-orange-colored crystals (390.9 mg, 94%).

30 $^1\text{H-NMR}$ (200 MHz, CD_3OD) δ : 1.90-2.20 (2H, m), 2.20-2.50 (2H, m), 3.15-4.10 (12H, m), 4.40-4.60 (2H, m), 6.50-6.70 (1H, m), 6.90-7.10 (2H, m), 7.30-7.70 (7H, m).

35 IR (KBr): 3425, 3064, 2949, 2603, 1633, 1566, 1535, 1500, 1454, 1389, 1296, 1215, 785, 700, 631, 599, 525 cm^{-1} .

Elemental analysis for $\text{C}_{25}\text{H}_{32}\text{N}_5\text{OSCl}, \cdot 1.5\text{H}_2\text{O}$
35 Calcd.: C, 51.42; H, 6.04; N, 11.99
Found : C, 51.20; H, 5.96; N, 11.75

Example 65

Synthesis of N-[3-(4-phenethyl-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride

5 1) The procedure of Example 64-3) was generally followed to provide N-[3-(4-phenethyl-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as deep-red solid.

10 $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 1.60-1.75 (2H, m), 1.80-1.95 (2H, m), 2.60-2.90 (14H, m), 3.35-3.50 (2H, m), 5.71 (1H, d, $J=6.6$ Hz), 6.50-6.70 (3H, m), 6.97 (1H, s), 7.10-7.35 (5H, m), 8.25-8.35 (1H, m).
IR (KBr): 3269, 3055, 2933, 2806, 1643, 1620, 1556, 1514, 1481, 1454, 1369, 1282, 1225, 1151, 1117, 777, 750, 700, 669 cm^{-1} .

15 2) The procedure of Example 64-4) was generally followed to provide N-[3-(4-phenethyl-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride
20 as orange-colored crystals.

25 $^1\text{H-NMR}$ (200 MHz, CD_3OD) δ : 1.95-2.20 (2H, m), 2.30-2.50 (2H, m), 3.10-3.25 (2H, m), 3.25-4.10 (14H, m), 6.62 (1H, d, $J=7.6$ Hz), 6.97-7.03 (2H, m), 7.20-7.45 (6H, m), 7.54 (1H, s).
IR (KBr): 3425, 3062, 2945, 2659, 2727, 1632, 1564, 1537, 1502, 1456, 1392, 1296, 1215, 1107, 785, 702 cm^{-1} .

Elemental analysis for $\text{C}_{26}\text{H}_{34}\text{N}_5\text{OSCl}_3 \cdot 2.0\text{H}_2\text{O}$

30 Calcd.: C, 51.44; H, 6.31; N, 11.54
Found : C, 51.48; H, 6.24; N, 11.62

Example 66

Synthesis of N-[3-(4-(3-phenylpropan-1-yl)-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride

35 1) The procedure of Example 64-3) was generally

followed to provide N-[3-(4-(3-phenylpropan-1-yl)-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as deep red oil.

5 ¹H-NMR (200 MHz, CDCl₃) δ: 1.60-1.95 (6H, m), 2.45-2.80
 (14H, m), 3.37-3.45 (2H, m), 5.72 (1H, dd, J=1.4,
 6.4 Hz), 6.52-6.66 (3H, m), 6.98 (1H, s), 7.10-
 7.35 (5H, m), 8.36 (1H, br s).
IR (neat): 3280, 3059, 3024, 2937, 2818, 1616, 1545,
10 1481, 1342, 1281, 1215, 1155, 1120, 1034, 966,
 868, 752, 700, 652, 606, 503, 473 cm⁻¹.

15 2) The procedure of Example 64-4) was generally followed to provide N-[3-(4-(3-phenylpropan-1-yl)-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride as light-orange-colored crystals.

15 ¹H-NMR (200 MHz, CD₃OD) δ: 1.95-2.55 (6H, m), 2.65-2.90
 (2H, m), 3.20-4.20 (14H, m), 6.50-6.70 (1H, m),
 6.90-7.15 (2H, m), 7.15-7.45 (6H, m), 7.50-7.60
20 (1H, m).
IR (KBr): 3394, 3061, 2947, 2659, 1633, 1564, 1537,
 1502, 1456, 1392, 1296, 1215, 1107, 787, 756, 702
 cm⁻¹.

25 Elemental analysis for C₂₇H₃₆N₅OSCl₃•1.0H₂O
Calcd.: C, 52.98; H, 6.42; N, 11.44
Found : C, 52.79; H, 6.61; N, 11.37

Example 67

Synthesis of N-[1-(3-(2-fluorophenyl)propan-1-yl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

30 1) Synthesis of N-[1-(3-(2-fluorophenyl)propan-1-yl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

35 Under nitrogen gas, 0.38 ml (4.90 mM) of methane-sulfonyl chloride was added to a solution of 499 mg (3.24 mM) of 2-fluorophenylpropanol and 0.90 ml (6.47

mM) of triethylamine in methylene chloride (6 ml) at 0°C and the mixture was stirred at the prevailing temperature for 20 minutes. The reaction was stopped by adding saturated aqueous solution of sodium hydrogen carbonate. The reaction mixture was then extracted with diethyl ether. The organic layer was washed with water and saturated aqueous solution of sodium chloride and dried over MgSO₄. The solvent was then distilled off under reduced pressure to provide 0.722 g (3.24 mM) of 2-fluorophenylpropyl mesylate. To a solution of 0.58 g (1.5 mM) of N-(piperidin-4-ylmethyl)-5-thia-1,8b-diazaacacenaphthylene-4-carboxamide dihydrochloride and 1.0 ml (7.2 mM) of triethylamine in ethanol was added 0.60 g (2.69 mM) of 2-fluorophenylpropyl mesylate at room temperature, and the mixture was refluxed under nitrogen for 16 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The resulting crude product was purified by column chromatography (methanol/ethyl acetate 20-50%) to provide the title compound.

Reddish purple amorphous substance. Yield 347 mg (54%)
25 ¹H-NMR (200 MHz, CDCl₃) δ: 1.21-2.05 (m, 9H), 2.38 (t, J=7.7 Hz, 2H), 2.65 (t, J=7.5 Hz, 2H), 2.94 (br d, J=11.8 Hz, 2H), 3.20 (t, J=6.1 Hz, 2H), 5.78 (dd, J=1.8, 6.0 Hz, 1H), 5.89-6.03 (m, 1H), 6.57-6.69 (m, 3H), 6.92-7.21 (m, 5H).

30 2) Synthesis of N-[1-(3-(2-fluorophenyl)propan-1-yl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacacenaphthylene-4-carboxamide dihydrochloride

To a solution of 347 mg (0.8 mM) of N-[1-(3-(2-fluorophenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacacenaphthylene-4-carboxamide in ethanol (4 ml) was added 1.0 ml (4.0 mM) of 4N-HCl/methanol.

After the solvent was distilled off under reduced pressure, ethanol and diethyl ether were added to the residue and the resulting crystals were collected by filtration and rinsed with ethanol and diethyl ether to provide the title compound.

5 Orange-colored crystals. Yield 360 mg (86%)
¹H-NMR (200 MHz, DMSO-d₆) δ: 1.36-2.09 (m, 7H), 2.66
(t, J=7.9 Hz, 2H), 2.72-3.48 (m, 8H), 6.57 (d,
J=7.4 Hz, 1H), 6.95 (d, J=8.8 Hz, 1H), 7.11-7.39
10 (m, 6H), 7.61 (s, 1H), 8.83-8.90 (m, 1H).
IR (KBr): 3462, 3057, 2951, 2696, 1643, 1535, 1497,
1443, 1290, 1221, 800 cm⁻¹.

Elemental analysis for C₂₅H₂₉N₄OSCl₂F•1.0H₂O
Calcd.: C, 55.45; H, 5.77; N, 10.35
15 Found : C, 55.60; H, 5.80; N, 10.13

Example 68

Synthesis of N-[1-(2-fluorophenethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

20 1) The procedure of Example 67-1) was generally followed to provide N-[1-(2-fluorophenethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as rouge-colored solid.
¹H-NMR (200 MHz, CDCl₃) δ: 1.20-1.45 (2H, m), 1.45-1.80
25 (3H, m), 1.95-2.15 (2H, m), 2.50-2.65 (2H, m), 2.82-2.90 (2H, m), 3.04 (2H, br d, J=11.8 Hz), 3.22 (2H, t, J=6.0 Hz), 5.79 (1H, dd, J=1.8, 6.2 Hz), 5.85-5.95 (1H, m), 6.59-6.71 (3H, m), 6.96-7.24 (5H, m).
30 IR (KBr): 3250, 3086, 2927, 1639, 1618, 1558, 1485, 1286, 1153, 760 cm⁻¹.
2) The procedure of Example 67-2) was generally followed to provide N-[1-(2-fluorophenethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as light-orange-colored crystals.

¹H-NMR (200 MHz, CD₃OD) δ: 1.45-1.70 (2H, m), 1.80-2.10
(3H, m), 2.95-3.50 (8H, m), 3.71 (2H, br d, J=12.4
Hz), 6.60 (1H, d, J=7.6 Hz), 6.99 (1H, d, J=7.8
Hz), 7.01 (1H, s), 7.07-7.20 (2H, m), 7.27-7.43
5 (3H, m), 7.52 (1H, s).
IR (KBr): 3427, 3250, 2933, 2688, 1635, 1566, 1539,
1497, 1439, 1390, 1284, 1209, 779, 761 cm⁻¹.
Elemental analysis for C₂₄H₂₇N₄OSFCl₂•0.5H₂O
Calcd.: C, 55.60; H, 5.44; N, 10.81
10 Found : C, 55.42; H, 5.40; N, 10.73
Example 69
Synthesis of N-[1-(3-fluorophenethyl)piperidin-4-yl-
methyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
dihydrochloride
15 1) The procedure of Example 67-1) was generally
followed to provide N-[1-(3-fluorophenethyl)piperidin-
4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-
carboxamide as rouge-colored solid.
¹H-NMR (200 MHz, CDCl₃) δ: 1.20-1.45 (2H, m), 1.45-1.80
20 (3H, m), 1.90-2.10 (2H, m), 2.55-2.63 (2H, m),
2.77-2.85 (2H, m), 3.01 (2H, br d, J=11.4 Hz),
3.21 (2H, t, J=6.0 Hz), 5.78 (1H, dd, J=2.2, 5.5
Hz), 6.20 (1H, br t, J=5.5 Hz), 6.57-6.69 (3H, m),
6.85-7.02 (4H, m), 7.18-7.25 (1H, m).
25 IR (KBr): 3315, 2924, 1618, 1547, 1483, 1281, 1148,
775, 733, 692 cm⁻¹.
2) The procedure of Example 67-2) was generally
followed to provide N-[1-(3-fluorophenethyl)piperidin-
4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-
30 carboxamide dihydrochloride as orange-colored crystals.
¹H-NMR (200 MHz, CD₃OD) δ: 1.45-1.70 (2H, m), 1.75-2.10
(3H, m), 2.90-3.50 (8H, m), 3.60-3.75 (2H, m),
6.62 (1H, d, J=7.6 Hz), 6.95-7.20 (5H, m), 7.30-
7.43 (2H, m), 7.53 (1H, s).
35 IR (KBr): 1633, 1566, 1539, 1292, 785 cm⁻¹.

Elemental analysis for $C_{24}H_{27}N_4OSFCl_2 \cdot 1.5H_2O$

Calcd.: C, 53.73; H, 5.64; N, 10.44

Found : C, 53.54; H, 5.91; N, 10.36

Example 70

5 Synthesis of N-[1-(4-fluorophenethyl)piperidin-4-yl-methyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

10 1) The procedure of Example 67-1) was generally followed to provide N-[1-(4-fluorophenethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as reddish orange-colored amorphous substance.

15 1H -NMR (200 MHz, CDCl₃) δ: 1.20-1.45 (2H, m), 1.45-1.80 (3H, m), 1.90-2.10 (2H, m), 2.50-2.59 (2H, m), 2.74-2.82 (2H, m), 3.01 (2H, br d, J=11.8 Hz), 3.21 (2H, t, J=6.0 Hz), 5.78 (1H, dd, J=2.0, 5.6 Hz), 6.09 (1H, br t, J=5.6 Hz), 6.58-6.69 (3H, m), 6.91-7.03 (3H, m), 7.11-7.27 (2H, m).
IR (KBr): 3352, 2927, 1618, 15456, 1510, 1481, 1282, 20 1219, 1153, 827, 773, 731 cm⁻¹.

20 2) The procedure of Example 67-2) was generally followed to provide N-[1-(4-fluorophenethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

25 1H -NMR (200 MHz, CD₃OD) δ: 1.45-1.75 (2H, m), 1.75-2.10 (3H, m), 2.90-3.45 (8H, m), 3.60-3.75 (2H, m), 6.61 (1H, d, J=7.8 Hz), 6.97-7.11 (4H, m), 7.29-7.42 (3H, m), 7.52 (1H, s).
IR (KBr): 3431, 3246, 3061, 2935, 2690, 1632, 1566,

30 1541, 1510, 1439, 1389, 1288, 1215, 831, 783 cm⁻¹.

Elemental analysis for $C_{24}H_{27}N_4OSFCl_2 \cdot 0.5H_2O$

Calcd.: C, 55.60; H, 5.44; N, 10.81

Found : C, 55.83; H, 5.27; N, 11.02

Example 71

35 Synthesis of N-[1-(2-chlorophenethyl)piperidin-4-yl-methyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

dihydrochloride

1) The procedure of Example 67-1) was generally followed to provide N-[1-(2-chlorophenethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as reddish orange-colored amorphous substance.

5 ¹H-NMR (200 MHz, CDCl₃) δ: 1.25-1.47 (2H, m), 1.47-1.80 (3H, m), 2.00-2.20 (2H, m), 2.56-2.64 (2H, m), 2.90-3.09 (4H, m), 3.23 (2H, t, J=5.8 Hz), 5.79 (1H, dd, J=1.8, 6.0 Hz), 5.94 (1H, br t, J=5.5 Hz), 6.59-6.71 (3H, m), 7.05 (1H, s), 7.10-7.40 (4H, m).
10 IR (KBr): 3309, 2924, 1618, 1543, 1510, 1479, 1282, 1155, 771, 754, 732 cm⁻¹.

15 2) The procedure of Example 67-2) was generally followed to provide N-[1-(2-chlorophenethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

20 ¹H-NMR (200 MHz, CD₃OD) δ: 1.45-1.75 (2H, m), 1.80-2.10 (3H, m), 2.95-3.45 (8H, m), 3.65-3.80 (2H, m), 6.61 (1H, d, J=7.8 Hz), 6.99 (1H, d, J=7.8 Hz), 7.01 (1H, s), 7.25-7.50 (5H, m), 7.53 (1H, s).
IR (KBr): 3429, 2945, 2710, 1653, 1635, 1564, 1537, 1502, 1282, 773, 754 cm⁻¹.

25 Elemental analysis for C₂₄H₂₇N₄OSCl₃•0.5H₂O
Calcd.: C, 53.89; H, 5.28; N, 10.47
Found : C, 53.74; H, 5.09; N, 10.52

Example 72

30 Synthesis of N-[1-(3-chlorophenethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

35 1) The procedure of Example 67-1) was generally followed to provide N-[1-(3-chlorophenethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as reddish orange-colored amorphous substance.

5 ¹H-NMR (200 MHz, CDCl₃) δ: 1.20-1.45 (2H, m), 1.45-1.80
 (3H, m), 1.90-2.15 (2H, m), 2.53-2.60 (2H, m),
 2.74-2.82 (2H, m), 3.00 (2H, br d, J=11.8 Hz),
 3.21 (2H, t, J=6.0 Hz), 5.78 (1H, dd, J=1.8, 6.0
 Hz), 5.95-6.05 (1H, m), 6.58-6.69 (3H, m), 7.03-
 7.09 (2H, m), 7.10-7.20 (3H, m).
IR (KBr): 3327, 2926, 1618, 1545, 1481, 1282, 1153, 687
cm⁻¹.
10 2) The procedure of Example 67-2) was generally
 followed to provide N-[1-(3-chlorophenethyl)piperidin-
 4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-
 carboxamide dihydrochloride as orange-colored crystals.
15 ¹H-NMR (200 MHz, CD₃OD) δ: 1.45-1.75 (2H, m), 1.75-2.10
 (3H, m), 2.90-3.50 (8H, m), 3.60-3.75 (2H, m),
 6.62 (1H, d, J=7.6 Hz), 6.97-7.02 (2H, m), 7.20-
 7.45 (5H, m), 7.53 (1H, s).
IR (KBr): 1633, 1566, 1537, 1504, 1292, 1215, 785 cm⁻¹.
Elemental analysis for C₂₄H₂₇N₄OSCl₃•1.5H₂O
Calcd.: C, 52.13; H, 5.47; N, 10.13
20 Found : C, 52.47; H, 5.53; N, 10.23

Example 73.
Synthesis of N-[1-(4-chlorophenethyl)piperidin-4-yl-
methyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
dihydrochloride
25 1) The procedure of Example 67-1) was generally
 followed to provide N-[1-(4-chlorophenethyl)piperidin-
 4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-
 carboxamide as reddish orange-colored amorphous
 substance.
30 ¹H-NMR (200 MHz, CDCl₃) δ: 1.20-1.45 (2H, m), 1.45-1.80
 (3H, m), 1.90-2.10 (2H, m), 2.50-2.60 (2H, m),
 2.70-2.85 (2H, m), 3.00 (2H, br d, J=11.4 Hz),
 3.22 (2H, t, J=6.1 Hz), 5.79 (1H, dd, J=1.9, 6.1
 Hz), 5.94 (1H, br t, J=5.9 Hz), 6.59-6.72 (3H, m),
 7.05-7.14 (3H, m), 7.22-7.27 (2H, m).
35 IR (KBr): 3282, 3055, 2924, 2806, 1616, 1549, 1485,

1282, 1153, 1119, 1092, 970, 773, 731 cm⁻¹.

- 2) The procedure of Example 67-2) was generally followed to provide N-[1-(4-chlorophenethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.
- 5 ¹H-NMR (200 MHz, CD₃OD) δ: 1.40-1.75 (2H, m), 1.75-2.10 (3H, m), 2.90-3.50 (8H, m), 3.60-3.75 (2H, m), 6.61 (1H, d, J=7.4 Hz), 6.99 (1H, d, J=8.8 Hz), 7.00 (1H, s), 7.25-7.45 (5H, m), 7.53 (1H, s).
- 10 IR (KBr): 3425, 3061, 2935, 2731, 1633, 1566, 1537, 1498, 1292, 1215, 785 cm⁻¹.

Elemental analysis for C₂₄H₂₇N₄O₂Cl₂•1.5H₂O

Calcd.: C, 52.13; H, 5.47; N, 10.13
Found : C, 51.90; H, 5.54; N, 10.10

15 Example 74

Synthesis of N-[1-(3-(3-fluorophenyl)propan-1-yl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

- 1) The procedure of Example 67-1) was generally followed to provide N-[1-(3-(3-fluorophenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.
- 20 ¹H-NMR (200 MHz, CDCl₃) δ: 1.30-1.97 (m, 9H), 2.31-2.38 (m, 2H), 2.62 (t, J=7.5 Hz, 2H), 2.93 (br d, J=11.8 Hz, 2H), 3.21 (t, J=6.0 Hz, 2H), 5.79 (dd, J=1.7, 6.1 Hz, 1H), 5.77-5.85 (m, 1H), 6.58-6.70 (m, 3H), 6.81-6.96 (m, 3H), 7.05 (s, 1H), 7.11-7.25 (m, 1H).
- 25 30 2) The procedure of Example 67-2) was generally followed to provide N-[1-(3-(3-fluorophenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.
- 35 30 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.45-2.13 (m, 7H), 2.66 (t, J=7.6 Hz, 2H), 2.70-3.28 (m, 8H), 6.62 (d,

J=7.2 Hz, 1H), 6.93-7.40 (m, 7H), 7.66 (s, 1H),
8.86-8.97 (m, 1H).

IR (KBr): 3417, 3064, 2941, 1635, 1574, 1535, 1294, 787
cm⁻¹.

5 Example 75

Synthesis of N-[1-(3-(4-fluorophenyl)propan-1-yl)-
piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-
4-carboxamide dihydrochloride

10 1) The procedure of Example 67-1) was generally
followed to provide N-[1-(3-(4-fluorophenyl)propan-1-
y1)piperidin-4-ylmethyl]-5-thia-1,8b-
diazaacenaphthylene-4-carboxamide as red-purple
amorphous substance.

15 ¹H-NMR (200 MHz, CDCl₃) δ: 1.30-2.47 (m, 11H), 2.61 (t,
J=7.7 Hz, 2H), 3.02 (br d, J=12 Hz, 2H), 3.21 (t,
J=5.9 Hz, 2H), 5.76-5.80 (m, 1H), 6.04-6.20 (m,
1H), 6.57-6.68 (m, 2H), 6.74 (s, 1H), 6.92-7.17
(m, 5H).

20 2) The procedure of Example 67-2) was generally
followed to provide N-[1-(3-(4-fluorophenyl)propan-1-
y1)piperidin-4-ylmethyl]-5-thia-1,8b-
diazaacenaphthylene-4-carboxamide dihydrochloride as
orange-colored crystals.

25 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40-2.04 (m, 6H), 2.53-
3.10 (m, 11H), 6.55 (d, J=7.6 Hz, 1H), 6.94 (d,
J=9.2 Hz, 1H), 7.08-7.31 (m, 6H), 7.57 (d, J=1.2
Hz, 1H), 8.78-8.88 (m, 1H).

IR (KBr): 1639, 1508, 1294, 1221 cm⁻¹.

Elemental analysis for C₂₅H₂₉N₄O₂SCl₂F•0.5H₂O

30 Calcd.: C, 56.39; H, 5.68; N, 10.52
Found : C, 56.47; H, 5.85; N, 10.61

Example 76

Synthesis of N-[1-(3-(2,4-difluorophenyl)propan-1-yl)-
piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-
4-carboxamide dihydrochloride

35 1) The procedure of Example 67-1) was generally

followed to provide N-[1-(3-(2,4-difluorophenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

5 $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 1.16-2.05 (m, 8H), 2.34 (t, $J=7.7$ Hz, 2H), 2.60 (t, $J=7.7$ Hz, 2H), 2.69 (m, 1H), 2.91 (br d, $J=12$ Hz, 2H), 3.18 (t, $J=6.1$ Hz, 2H), 5.76 (dd, $J=2.8, 5.0$ Hz, 1H), 6.39 (m, 1H), 6.56-6.82 (m, 5H), 6.98 (s, 1H), 7.07-7.18 (m, 1H).

10 2) The procedure of Example 67-2) was generally followed to provide N-[1-(3-(2,4-difluorophenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

15 $^1\text{H-NMR}$ (200 MHz, DMSO-d_6) δ : 1.35-2.06 (m, 7H), 2.60-3.49 (m, 10H), 6.56 (d, $J=7.6$ Hz, 1H), 6.95 (d, $J=8.8$ Hz, 1H), 7.00-7.46 (m, 5H), 7.60 (s, 1H), 8.82-8.90 (m, 1H).

20 IR (KBr): 3415, 3056, 2943, 2700, 1635, 1504, 1288 cm^{-1} .
Elemental analysis for $\text{C}_{25}\text{H}_{28}\text{N}_4\text{OSCl}_2\text{F}_2 \cdot 1.0\text{H}_2\text{O}$

Calcd.: C, 53.67; H, 5.40; N, 10.01

Found : C, 53.97; H, 5.28; N, 10.11

Example 77

25 Synthesis of N-[1-(3-(2-chlorophenyl)propan-1-yl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) The procedure of Example 67-1) was generally followed to provide N-[1-(3-(2-chlorophenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

30 $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 1.17-2.05 (m, 9H), 2.39 (t, $J=7.6$ Hz, 2H), 2.74 (t, $J=7.7$ Hz, 2H), 2.94 (br d, $J=11.4$ Hz, 2H), 3.20 (t, $J=6.1$ Hz, 2H), 5.78 (dd, $J=1.8, 6.0$ Hz, 1H), 5.97 (m, 1H), 6.57-6.70 (m,

3H), 7.03 (s, 1H), 7.06-7.37 (m, 4H).

2) The procedure of Example 67-2) was generally followed to provide N-[1-(3-(2-chlorophenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

5 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40-2.23 (m, 7H), 2.65-3.70 (m, 10H), 6.49-6.53 (d, J=7.4 Hz, 1H), 6.92 (d, J=9.4 Hz, 1H), 7.08-7.46 (m, 6H), 7.55 (s, 1H), 8.75-8.80 (m, 1H).

10 IR (KBr): 3452, 3375, 3055, 2951, 2690, 1641, 1531, 1439, 1288, 1217, 800 cm⁻¹.

Elemental analysis for C₂₅H₂₉N₄OSCl₂•0.6H₂O

Calcd.: C, 54.51; H, 5.52; N, 10.17

15 Found : C, 54.70; H, 5.71; N, 9.90

Example 78

Synthesis of N-[1-(3-(3-chlorophenyl)propan-1-yl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

20 1) The procedure of Example 67-1) was generally followed to provide N-[1-(3-(3-chlorophenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

25 ¹H-NMR (200 MHz, CDCl₃) δ: 1.18-2.00 (m, 9H), 2.29-2.37 (m, 2H), 2.59 (t, J=7.5 Hz, 2H), 2.91 (br d, J=11.4 Hz, 2H), 3.18 (t, J=6.1 Hz, 2H), 5.76 (dd, J=2.4, 5.4 Hz, 1H), 6.29 (br t, J=5.9 Hz, 1H), 6.59-6.66 (m, 3H), 7.00 (s, 1H), 7.03-7.07 (m, 1H), 7.12-7.24 (m, 3H).

30 2) The procedure of Example 67-2) was generally followed to provide N-[1-(3-(3-chlorophenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

35 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40-2.12 (m, 7H), 2.65

(t, J=7.7 Hz, 2H), 2.72-3.26 (m, 6H), 3.38-3.50 (m, 2H), 6.61 (d, J=7.4 Hz, 1H), 6.97 (d, J=9.2 Hz, 1H), 7.21-7.39 (m, 6H), 7.65 (s, 1H), 8.89-8.99 (m, 1H).

5. IR (KBr): 3442, 1637, 1292, 1213, 793 cm⁻¹.

Elemental analysis for C₂₅H₂₉N₄OSCl₃•1.0H₂O

Calcd.: C, 53.82; H, 5.60; N, 10.04

Found : C, 54.07; H, 5.80; N, 9.79

Example 79

10 Synthesis of N-[1-[3-(4-chlorophenyl)propan-1-yl]-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

15 1) The procedure of Example 67-1) was generally followed to provide N-[1-[3-(4-chlorophenyl)propan-1-yl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red oil.

20 ¹H-NMR (200 MHz, CDCl₃) δ: 1.45-1.83 (5H, m), 1.85-2.03 (2H, m), 2.15-2.30 (2H, m), 2.53-2.67 (4H, m), 3.10-3.24 (4H, m), 5.754 (1H, dd, J=2.4, 5.3 Hz), 6.50-6.70 (3H, m), 6.822 (1H, s), 7.05-7.15 (3H, m), 7.22-7.30 (2H, m).

25 2) The procedure of Example 67-2) was generally followed to provide N-[1-[3-(4-chlorophenyl)propan-1-yl]piperidin-4-ylmethyl]-5-thia-1,8b-

diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

30 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.45-1.95 (4H, m), 1.90-2.15 (2H, m), 2.58-2.70 (2H, m), 2.70-3.30 (5H, m), 3.40-3.55 (2H, m), 6.685 (1H, d, J=7.6 Hz), 7.017 (1H, d, J=7.6 Hz), 7.017 (1H, d, J=9.2 Hz), 7.24-7.39 (5H, m), 7.720 (1H, s), 8.90-9.10 (1H, m), 10.588 (1H, br s).

35 IR (KBr): 3420, 3250, 3050, 2950, 2850, 2720, 2670, 2600, 2550, 1650, 1630, 1560, 1530, 1500, 1440, 1280, 1220, 1090, 780 cm⁻¹.

Elemental analysis for C₂₅H₂₉N₄OSCl₃•1.5H₂O

Calcd.: C, 52.96; H, 5.69; N, 9.88

Found : C, 53.43; H, 5.71; N, 9.59

Example 80

Synthesis of N-[1-(3-(2-methoxyphenyl)propan-1-yl)-
5 piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-
4-carboxamide dihydrochloride

1) The procedure of Example 67-1) was generally
followed to provide N-[1-(3-(2-methoxyphenyl)propan-1-
yl)piperidin-4-ylmethyl]-5-thia-1,8b-
10 diazaacenaphthylene-4-carboxamide as red-purple
amorphous substance.

¹H-NMR (200 MHz, CDCl₃) δ: 1.20-2.00 (m, 9H), 2.35-2.43
(m, 2H), 2.61 (t, J=7.7 Hz, 2H), 2.96 (br d,
J=11.4 Hz, 2H), 3.18 (t, J=5.9 Hz, 2H), 3.81 (s,
15 3H), 5.74-5.78 (m, 1H), 6.16-6.30 (m, 1H), 6.55-
6.67 (m, 3H), 6.78-6.89 (m, 2H), 6.99-7.20 (m,
3H).

2) The procedure of Example 67-2) was generally
followed to provide N-[1-(3-(2-methoxyphenyl)propan-1-
20 yl)piperidin-4-ylmethyl]-5-thia-1,8b-
diazaacenaphthylene-4-carboxamide dihydrochloride as
orange-colored crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.35-2.00 (m, 7H), 2.53-
3.26 (m, 8H), 3.38-3.47 (m, 2H), 3.79 (s, 3H),
25 6.56 (d, J=7.2 Hz, 1H), 6.83-6.98 (m, 3H), 7.13-
7.27 (m, 4H), 7.60 (s, 1H), 8.80-8.92 (m, 1H).

IR (KBr): 3463, 3390, 2948, 2702, 1638, 1533, 1498,
1441, 1290, 802, 764 cm⁻¹.

Elemental analysis for C₂₆H₃₂N₄OSCl₂•1.0H₂O

30 Calcd.: C, 56.41; H, 6.19; N, 10.12

Found : C, 56.69; H, 6.24; N, 10.07

Example 81

Synthesis of N-[1-[3-(4-methoxyphenyl)propan-1-yl]-
35 piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-
4-carboxamide dihydrochloride

1) The procedure of Example 67-1) was generally

followed to provide N-[1-[3-(4-methoxyphenyl)propan-1-yl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red oil.

5 ¹H-NMR (200 MHz, CDCl₃) δ: 1.25-1.95 (9H, m), 2.29-2.36 (2H, m), 2.52-2.60 (2H, m), 2.86-2.96 (2H, m), 3.204 (2H, t, J=6.2 Hz), 3.786 (3H, s), 5.791 (1H, dd, J=1.8, 6.2 Hz), 5.70-5.82 (1H, m), 6.632-6.692 (3H, m), 6.818 (2H, d, J=8.6 Hz), 7.054 (1H, s), 7.093 (2H, d, J=8.8 Hz).

10 2) The procedure of Example 67-2) was generally followed to provide N-[1-[3-(4-methoxyphenyl)propan-1-yl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

15 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.45-2.10 (7H, m), 2.50-2.60 (2H, m), 2.70-3.30 (6H, m), 3.37-3.51 (2H, m), 3.728 (3H, s), 6.604 (1H, d, J=7.4 Hz), 6.867 (2H, d, J=8.0 Hz), 6.973 (1H, d, J=9.2 Hz), 7.13-7.32 (4H, m), 7.643 (1H, s), 8.90-8.96 (1H, m).

20 IR (KBr): 3420, 3280, 2980, 2930, 2670, 1635, 1560, 1530, 1510, 1460, 1280, 1260, 1240, 1220, 1030, 780 cm⁻¹.

Elemental analysis for C₂₆H₃₂N₄O₂SCl₂•1H₂O

Calcd.: C, 56.41; H, 6.19; N, 10.12

25 Found : C, 56.09; H, 6.36; N, 10.00

Example 82

Synthesis of N-[1-(3-(2,3-dimethoxyphenyl)propan-1-yl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

30 1) The procedure of Example 67-1) was generally followed to provide N-[1-(3-(2,3-dimethoxyphenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

35 ¹H-NMR (200 MHz, CDCl₃) δ: 1.15-1.98 (m, 9H), 2.34-2.42 (m, 2H), 2.54-2.69 (m, 2H), 2.85-2.99 (m, 2H),

3.17 (t, J=6.0 Hz, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 5.73-5.78 (m, 1H), 6.52-6.65 (m, 4H), 6.75-6.79 (m, 2H), 6.92-6.99 (m, 2H).

2) The procedure of Example 67-2) was generally
5 followed to provide N-[1-(3-(2,3-dimethoxyphenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

10 $^1\text{H-NMR}$ (200 MHz, DMSO-d₆) δ: 1.35-2.03 (m, 7H), 2.55-3.07 (m, 8H), 3.38-3.49 (m, 2H), 3.73 (s, 3H), 3.80 (s, 3H), 6.58 (d, J=7.8 Hz, 1H), 6.78-7.03 (m, 4H), 7.14-7.29 (m, 2H), 7.61 (s, 1H), 8.81-8.90 (m, 1H).

15 Elemental analysis for C₂₇H₃₄N₄O₃SCl₂•2.0H₂O
Calcd.: C, 53.91; H, 6.37; N, 9.31
Found : C, 53.98; H, 6.66; N, 9.06

Example 83

Synthesis of N-[1-(3-(2,4-dimethoxyphenyl)propan-1-yl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

20 1) The procedure of Example 67-1) was generally followed to provide N-[1-(3-(2,4-dimethoxyphenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

25 $^1\text{H-NMR}$ (200 MHz, CDCl₃) δ: 1.20-1.97 (m, 9H), 2.33-2.41 (m, 2H), 2.53 (t, J=7.6 Hz, 2H), 2.95 (br d, J=11.4 Hz, 2H), 3.18 (t, J=6.0 Hz, 2H), 3.78 (s, 3H), 3.79 (s, 3H), 5.76 (dd, J=2.4, 5.6 Hz, 1H),
30 6.26-6.43 (m, 3H), 6.60-6.68 (m, 3H), 6.99-7.03 (m, 2H).

30 2) The procedure of Example 67-2) was generally followed to provide N-[1-(3-(2,4-dimethoxyphenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.39-1.95 (m, 7H), 2.65-3.25 (m, 8H), 3.37-3.45 (m, 2H), 3.74 (s, 3H), 3.78 (s, 3H), 6.43-6.55 (m, 3H), 6.92 (d, J=9.0 Hz, 1H), 7.04-7.24 (m, 3H), 7.57 (s, 1H), 8.77-8.84 (m, 1H).

5 IR (KBr): 3429, 1633, 1508, 1292, 1209, 787 cm⁻¹.

Elemental analysis for C₂₇H₃₄N₄O₃SCl₂•2.5H₂O

Calcd.: C, 53.11; H, 6.44; N, 9.18

Found : C, 53.30; H, 6.65; N, 9.18

10 Example 84

Synthesis of N-[1-[3-(4-ethylphenyl)propan-1-yl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) The procedure of Example 67-1) was generally followed to provide N-[1-[3-(4-ethylphenyl)propan-1-yl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red oil.

15 ¹H-NMR (200 MHz, CDCl₃) δ: 1.220 (3H, t, J=7.6 Hz), 1.25-1.38 (1H, m), 1.40-2.05 (8H, m), 2.32-2.39 (2H, m), 2.54-2.67 (4H, m), 2.88-2.95 (2H, m), 3.196 (2H, t, J=6.1 Hz), 5.778 (1H, dd, J=1.8, 6.1 Hz), 5.85-5.93 (1H, m), 6.573-6.695 (3H, m), 7.034 (1H, s), 7.097 (4H, s).

20 2) The procedure of Example 67-2) was generally followed to provide N-[1-[3-(4-ethylphenyl)propan-1-yl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

25 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.159 (3H, t, J=7.5 Hz), 1.43-1.85 (5H, m), 1.90-2.10 (2H, m), 2.45-2.65 (4H, m), 2.75-3.25 (5H, m), 3.35-3.55 (3H, m), 6.603 (1H, d, J=7.4 Hz), 6.970 (1H, d, J=9.2 Hz), 7.14-7.31 (5H, m), 7.643 (1H, s), 8.85-9.00 (1H, m), 10.47 (1H, br s).

30 35 IR (KBr): 3400, 3250, 3050, 2950, 2920, 2730, 1630, 1560, 1530, 1500, 1440, 1390, 1290, 1110, 1045,

945, 780 cm⁻¹.

Elemental analysis for C₂₇H₃₄N₄O₂SCl₂•1H₂O

Calcd.: C, 58.79; H, 6.58; N, 10.16

Found : C, 58.64; H, 6.62; N, 9.62

5 Example 85

Synthesis of N-[1-(3-(2-trifluoromethylphenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

10 1) The procedure of Example 67-1) was generally followed to provide N-[1-(3-(2-trifluoromethylphenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

15 ¹H-NMR (200 MHz, CDCl₃) δ: 1.18-2.05 (m, 9H), 2.30-2.38 (m, 2H), 2.68 (t, J=7.5 Hz, 2H), 2.85-3.01 (m, 2H), 3.21 (t, J=6.2 Hz, 2H), 5.79 (dd, J=1.8, 6.0 Hz, 1H), 5.65-5.90 (m, 1H), 6.59-6.71 (m, 3H), 7.05 (s, 1H), 7.28 (d, J=8.0 Hz, 2H), 7.53 (d, J=8.0 Hz, 2H).

20 2) The procedure of Example 67-2) was generally followed to provide N-[1-(3-(2-trifluoromethylphenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

25 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.30-2.10 (m, 7H), 2.68-3.52 (m, 10H), 6.51 (d, J=7.4 Hz, 1H), 6.91 (d, J=8.8 Hz, 1H), 7.08 (s, 1H), 7.14-7.22 (m, 1H), 7.41-7.73 (m, 5H), 8.72-8.86 (m, 1H).

30 IR (KBr): 3425, 3250, 3059, 2947, 2710, 1637, 1308, 1115, 779 cm⁻¹.

Elemental analysis for C₂₆H₂₉N₄OSCl₂F₃•1.5H₂O

Calcd.: C, 52.00; H, 5.37; N, 9.33

Found : C, 51.77; H, 5.28; N, 9.10

Example 86

35 Synthesis of N-[1-(3-(3-trifluoromethylphenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-

diazaacenaphthylene-4-carboxamide dihydrochloride

1) The procedure of Example 67-1) was generally followed to provide N-[1-(3-(3-trifluoromethylphenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

10 $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 1.18-2.03 (m, 9H), 2.30-2.37 (m, 2H), 2.68 (t, $J=7.6$ Hz, 2H), 2.88-2.94 (m, 2H), 3.20 (t, $J=6.0$ Hz, 2H), 5.78 (dd, $J=1.9, 5.9$ Hz, 1H), 6.07 (br t, $J=5.9$ Hz, 1H), 6.62-6.68 (m, 3H), 7.02 (s, 1H), 7.35-7.48 (m, 4H).

15 2) The procedure of Example 67-2) was generally followed to provide N-[1-(3-(3-trifluoromethylphenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

20 $^1\text{H-NMR}$ (200 MHz, DMSO-d_6) δ : 1.19-2.08 (m, 7H), 2.68-3.52 (m, 10H), 6.60 (d, $J=7.2$ Hz, 1H), 6.96 (d, $J=8.6$ Hz, 1H), 7.17-7.31 (m, 2H), 7.58-7.64 (m, 5H), 8.86-8.97 (m, 1H).

IR (KBr): 3423, 3060, 2942, 1637, 1329, 1120, 791 cm^{-1} .

Elemental analysis for $\text{C}_{26}\text{H}_{29}\text{N}_4\text{OSCl}_2\text{F}_3 \cdot 2.0\text{H}_2\text{O}$

Calcd.: C, 51.23; H, 5.46; N, 9.19

Found : C, 51.25; H, 5.45; N, 9.17

25 Example 87

Synthesis of N-[1-(3-(4-trifluoromethylphenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

30 1) The procedure of Example 67-1) was generally followed to provide N-[1-(3-(4-trifluoromethylphenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

35 $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 1.18-2.05 (m, 9H), 2.30-2.38 (m, 2H), 2.68 (t, $J=7.5$ Hz, 2H), 2.85-3.01 (m, 2H), 3.21 (t, $J=6.2$ Hz, 2H), 5.79 (dd, $J=1.8, 6.0$

Hz, 1H), 5.65-5.90 (m, 1H), 6.59-6.71 (m, 3H),
7.05 (s, 1H), 7.28 (d, J=8.0 Hz, 2H), 7.53 (d,
J=8.0 Hz, 2H).

2) The procedure of Example 67-2) was generally
5 followed to provide N-[1-(3-(4-
trifluoromethylphenyl)propan-1-yl)piperidin-4-
ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
dihydrochloride as orange-colored crystals.

10 $^1\text{H-NMR}$ (200 MHz, DMSO-d₆) δ: 1.36-2.18 (m, 7H), 2.74
(t, J=7.6 Hz, 2H), 2.70-3.23 (m, 6H), 3.41-3.53
(m, 2H), 6.64 (d, J=7.0 Hz, 1H), 6.99 (d, J=8.4
Hz, 1H), 7.16-7.23 (m, 1H), 7.30 (dd, J=7.0, 8.4
Hz, 1H), 7.49 (d, J=8.0 Hz, 2H), 7.677 (s, 1H),
2.782 (d, J=8.0 Hz, 2H), 8.87-9.00 (m, 1H).
15 IR (KBr): 3398, 3057, 2941, 2673, 1635, 1327, 1119, 785
 cm^{-1} .

Elemental analysis for C₂₆H₂₉N₄OSCl₂F₃•1.5H₂O

Calcd.: C, 52.00; H, 5.37; N, 9.33

Found : C, 51.87; H, 5.16; N, 9.47

20 Example 88

Synthesis of N-[1-(3-(3-trifluoromethoxyphenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) The procedure of Example 67-1) was generally
25 followed to provide N-[1-(3-(3-
trifluoromethoxyphenyl)propan-1-yl)piperidin-4-
ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
as red oil.

30 $^1\text{H-NMR}$ (200 MHz, CDCl₃) δ: 1.20-1.38 (2H, m), 1.42-1.60
(1H, m), 1.62-2.00 (6H, m), 2.335 (2H, t, J=7.5
Hz), 2.645 (2H, t, J=7.7 Hz), 2.915 (2H, d, J=11.8
Hz), 3.207 (2H, t, J=6.1 Hz), 5.790 (1H, dd,
J=1.8, 6.2 Hz), 5.78-5.85 (1H, m), 6.58-6.71 (3H,
m), 7.00-7.13 (4H, m), 7.23-7.339 (1H, m).

35 2) The procedure of Example 67-2) was generally
followed to provide N-[1-(3-(3-

trifluoromethoxyphenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.42-1.95 (5H, m), 1.95-5 2.15 (2H, m), 2.61-3.23 (8H, m), 3.451 (2H, d like, J=11.4 Hz), 6.685 (1H, d, J=7.6 Hz), 7.020 (1H, d, J=9.2 Hz), 7.15-7.50 (6H, m), 7.719 (1H, s), 9.065 (1H, t like, J=5.5 Hz), 10.5 (1H, br s). IR (KBr): 3420, 2950, 2720, 2550, 1635, 1565, 1535, 10 1500, 1440, 1395, 1280, 1220, 1150, 790, 740, 700, 630, 600 cm⁻¹.

Elemental analysis for C₂₆H₂₉N₄O₂SCl₂F₃•1.5H₂O

Calcd.: C, 50.65; H, 5.23; N, 9.09

Found : C, 50.32; H, 5.63; N, 8.81

15 Example 89

Synthesis of N-[1-(3-(4-trifluoromethoxyphenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) The procedure of Example 67-1) was generally 20 followed to provide N-[1-(3-(4-trifluoromethoxyphenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

¹H-NMR (200 MHz, CDCl₃) δ: 1.32-2.21 (m, 9H), 2.44-2.52 25 (m, 2H), 2.64 (t, J=7.6 Hz, 2H), 3.03-3.09 (m, 2H), 3.19 (t, J=5.5 Hz, 2H), 5.75 (dd, J=2.6, 5.4 Hz, 1H), 6.41-6.69 (m, 3H), 6.77 (s, 1H), 7.01-7.22 (m, 5H).

2) The procedure of Example 67-2) was generally 30 followed to provide N-[1-(3-(4-trifluoromethoxyphenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.38-2.16 (m, 7H), 2.67 35 (t, J=7.6 Hz, 2H), 2.70-3.26 (m, 6H), 3.38-3.52 (m, 2H), 6.62 (d, J=7.4 Hz, 1H), 6.98 (d, J=9.0

Hz, 1H), 7.19-7.41 (m, 6H), 7.65 (s, 1H), 8.90-8.96 (m, 1H).

IR (KBr): 3375, 3062, 2942, 2710, 1637, 1506, 1269, 1217, 1161, 787 cm⁻¹.

5 Elemental analysis for C₂₆H₂₉N₄O₂SCl₂F₃•1.5H₂O

Calcd.: C, 50.65; H, 5.23; N, 9.09

Found : C, 50.38; H, 5.20; N, 8.87

Example 90

10 Synthesis of N-[1-[3-(4-hydroxyphenyl)propan-1-yl]-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

15 1) The procedure of Example 67-1) was generally followed to provide N-[1-[3-(4-tert-butylidimethylsiloxyphenyl)propan-1-yl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red oil.

20 ¹H-NMR (200 MHz, CDCl₃) δ: 0.178 (6H, s), 0.978 (9H, s), 1.20-1.42 (2H, m), 1.42-2.05 (7H, m), 2.28-2.90 (2H, m), 2.544 (2H, t like, J=7.5 Hz), 2.88-3.00 (2H, m), 3.202 (2H, t like, J=6.0 Hz), 5.785 (1H, d, J=6.6 Hz), 5.80-5.95 (1H, m), 6.59-6.76 (5H, m), 6.90-7.05 (3H, m).

25 2) The procedure of Example 67-2) was generally followed to provide N-[1-[3-(4-hydroxyphenyl)propan-1-yl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

30 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40-2.10 (7H, m), 2.65-3.20 (7H, m), 3.33-3.53 (3H, m), 6.61-6.78 (3H, m), 6.90-7.05 (3H, m), 7.15-7.35 (2H, m), 7.671 (1H, s), 8.85-9.03 (1H, m), 10.4 (1H, br s).

IR (KBr): 3420, 3250, 2950, 2930, 1650, 1635, 1610, 1560, 1540, 1520, 1500, 1290, 1220, 800 cm⁻¹.

Elemental analysis for C₂₅H₃₀N₄O₂SCl₂•1.0H₂O

35 Calcd.: C, 55.66; H, 5.98; N, 10.38

Found : C, 55.81; H, 5.91; N, 10.07

Example 91

Synthesis of N-[1-(3-(4-biphenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

5 1) The procedure of Example 67-1) was generally followed to provide N-[1-(3-(4-biphenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

10 $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 1.33-2.16 (m, 9H), 2.49-2.56 (m, 2H), 2.68 (t, $J=7.7$ Hz, 2H), 3.08 (br d, $J=11.8$ Hz, 2H), 3.19 (t, $J=5.9$ Hz, 2H), 5.73 (dd, $J=2.2$, 5.6 Hz, 1H), 6.53-6.72 (m, 3H), 6.77 (s, 1H), 7.01 (s, 1H), 7.23-7.60 (m, 9H).

15 2) The procedure of Example 67-2) was generally followed to provide N-[1-(3-(4-biphenyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

20 $^1\text{H-NMR}$ (200 MHz, DMSO-d_6) δ : 1.35-2.17 (m, 7H), 2.60-3.52 (m, 10H), 6.52 (d, $J=7.4$ Hz, 1H), 6.92 (d, $J=8.2$ Hz, 1H), 7.10-7.66 (m, 12H), 8.72-8.84 (m, 1H).

IR (KBr): 3425, 1635, 1292, 1213, 775 cm^{-1}

25 Elemental analysis for $\text{C}_{31}\text{H}_{34}\text{N}_4\text{OSCl}_2 \cdot 2.0\text{H}_2\text{O}$

Calcd.: C, 60.28; H, 6.20; N, 9.07

Found : C, 60.10; H, 6.28; N, 8.79

Example 92

Synthesis of N-[1-(1-naphthylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

30 1) The procedure of Example 67-1) was generally followed to provide N-[1-(1-naphthylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as deep-red amorphous substance.

35 $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ : 1.15-1.40 (2H, m), 1.45-1.80

(3H, m), 1.90-2.10 (2H, m), 2.96 (2H, br d, J=11.0 Hz), 3.19 (2H, t, J=6.1 Hz), 3.88 (2H, s), 5.77 (1H, dd, J=1.5, 6.3 Hz), 5.75-5.90 (1H, m), 6.57-6.70 (3H, m), 7.04 (1H, s), 7.35-7.65 (4H, m),
5 7.70-7.90 (2H, m), 8.20-8.350 (1H, m).

IR (KBr): 3319, 3049, 2922, 2806, 2764, 1618, 1541, 1510, 1481, 1367, 1281, 1151, 1113, 970, 773, 733, 652 cm⁻¹.

2) The procedure of Example 67-2) was generally
10 followed to provide N-[1-(1-naphthylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as light-orange-colored crystals.

¹H-NMR (200 MHz, CD₃OD) δ: 1.35-1.65 (2H, m), 1.80-2.05 (3H, m), 3.10-3.40 (4H, m), 3.50-3.65 (2H, m),
15 4.83 (2H, s), 6.60 (1H, d, J=7.6 Hz), 6.95-7.00 (2H, m), 7.34-7.81 (6H, m), 7.98-8.08 (2H, m), 8.26 (1H, d, J=8.0 Hz).

IR (KBr): 3427, 3062, 2935, 2729, 1633, 1564, 1537, 1504, 1394, 1296, 1217, 779, 602 cm⁻¹.

20 Elemental analysis for C₂₇H₂₈N₄O₂SCl₂•4.0H₂O

Calcd.: C, 54.09; H, 6.05; N, 9.34

Found : C, 54.15; H, 5.79; N, 9.38

Example 93

Synthesis of N-[1-(2-naphthylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

25 1) The procedure of Example 67-1) was generally followed to provide N-[1-(2-naphthylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as reddish orange-colored solid.

30 ¹H-NMR (CDC) δ: 1.20-1.45 (2H, m), 1.45-1.75 (3H, m), 1.80-2.15 (2H, m), 2.95 (2H, br d, J=11.4 Hz), 3.20 (2H, t, J=5.9 Hz), 3.66 (2H, s), 5.77 (1H, d, J=6.2 Hz), 5.80-5.95 (1H, m), 6.57-6.70 (3H, m),
35 7.03 (1H, s), 7.40-7.55 (3H, m), 7.70-7.90 (4H, m).

IR (KBr): 3292, 3257, 3051, 2912, 2800, 1630, 1545, 1512, 1481, 1365, 1335, 1279, 1146, 771, 730 cm⁻¹.

2) The procedure of Example 67-2) was generally followed to provide N-[1-(2-naphthylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

10 ¹H-NMR (200 MHz, CD₃OD) δ: 1.40-1.70 (2H, m), 1.80-2.05 (3H, m), 2.95-3.30 (4H, m), 3.45-2.65 (2H, m), 4.48 (2H, s), 6.59 (1H, d, J=7.0 Hz), 6.96 (1H, s), 6.97 (1H, d, J=8.4 Hz), 7.33-7.41 (1H, m), 7.50 (1H, s), 7.50-7.65 (3H, m), 7.90-8.05 (3H, m), 8.07 (1H, s).

15 IR (KBr): 3427, 3228, 3055, 2933, 2669, 2530, 1632, 1566, 1537, 1502, 1433, 1389, 1290, 1213, 781, 598, 478 cm⁻¹.

Elemental analysis for C₂₇H₂₈N₄OSCl₂•1.0H₂O

Calcd.: C, 59.45; H, 5.54; N, 10.27

Found : C, 59.52; H, 5.54; N, 10.27

Example 94

20 Synthesis of N-[1-(3-(2-naphthyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) The procedure of Example 67-1) was generally followed to provide N-[1-(3-(2-naphthyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

25 ¹H-NMR (200 MHz, CDCl₃) δ: 1.35-1.81 (m, 5H), 1.97-2.21 (m, 4H), 2.55-2.64 (m, 2H), 3.03-3.22 (m, 6H), 30 5.73 (dd, J=2.0, 6.0 Hz, 1H), 6.51-6.63 (m, 3H), 6.79 (s, 1H), 7.01 (s, 1H), 7.27-7.54 (m, 4H), 7.71 (br d, J=8.0 Hz, 1H), 7.82-7.87 (m, 1H), 7.97-8.04 (m, 1H).

30 2) The procedure of Example 67-2) was generally followed to provide N-[1-(3-(2-naphthyl)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-

diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.39-1.71 (m, 5H), 2.03-2.23 (m, 2H), 2.70-3.28 (m, 8H), 3.37-3.50 (m, 2H), 6.60 (d, J=7.2 Hz, 1H), 6.97 (d, J=8.8 Hz, 1H), 7.20-7.31 (m, 2H), 7.40-7.58 (m, 4H), 7.65 (s, 1H), 7.78-7.83 (m, 1H), 7.91-7.96 (m, 1H), 8.09-8.13 (m, 1H), 8.90-9.01 (m, 1H).
IR (KBr): 3489, 3394, 3253, 2951, 2698, 1637, 1535, 1292, 1211, 793 cm⁻¹.

Elemental analysis for C₂₉H₃₂N₄OSCl₂•1.5H₂O

Calcd.: C, 59.79; H, 6.06; N, 9.62

Found : C, 59.65; H, 6.06; N, 9.46

Example 95

15 Synthesis of N-[1-[2-(thiophen-2-yl)ethan-1-yl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) The procedure of Example 67-1) was generally followed to provide N-[1-[2-(thiophen-2-yl)ethan-1-yl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red solid.

¹H-NMR (200 MHz, CDCl₃) δ: 1.23-1.41 (2H, m), 1.45-1.8 (3H, m), 1.95-2.13 (2H, m), 2.58-2.68 (2H, m), 2.96-3.08 (4H, m), 3.212 (2H, t, J=6.1 Hz), 5.789 (1H, dd, J=1.9, 5.9 Hz), 5.95-6.09 (1H, m), 6.58-6.71 (3H, m), 6.81-6.94 (1H, m), 7.035 (1H, s), 7.129 (1H, dd, J=1.0, 5.0 Hz).

2) The procedure of Example 67-2) was generally followed to provide N-[1-[2-(thiophen-2-yl)ethan-1-yl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40-1.95 (5H, m), 2.80-3.10 (4H, m), 3.15-3.40 (4H, m), 3.549 (2H, d like, J=12.2 Hz), 6.633 (1H, d, J=7.4 Hz), 6.96-7.03 (3H, m), 7.227 (1H, s), 7.22-7.34 (1H, m),

7.420 (1H, d, J=4.8 Hz), 7.672 (1H, s), 8.95-9.00
(1H, m), 10.83 (1H, br s).

IR (KBr): 3430, 3250, 3050, 2930, 2700, 1635, 1585,
1540, 1500, 1440, 1390, 1290, 1280, 1210, 780, 700
cm⁻¹.

5 Elemental analysis for C₂₂H₂₆N₄OS₂Cl₂•0.5H₂O

Calcd.: C, 52.17; H, 5.37; N, 11.06

Found : C, 52.05; H, 5.56; N, 10.88

Example 96

10 Synthesis of N-[1-[2-(thiophen-3-yl)ethan-1-
yl]piperidin-4-ylmethyl]-5-thia-1,8b-
diazaacenaphthylene-4-carboxamide dihydrochloride

15 1) The procedure of Example 67-1) was generally
followed to provide N-[1-[2-(thiophen-3-yl)ethan-1-
yl]piperidin-4-ylmethyl]-5-thia-1,8b-
diazaacenaphthylene-4-carboxamide as red solid.

20 ¹H-NMR (200 MHz, CDCl₃) δ: 1.21-1.45 (2H, m), 1.45-1.68
(1H, m), 1.68-1.88 (2H, m), 1.93-2.08 (2H, m),
2.56-2.68 (2H, m), 2.80-2.88 (2H, m), 3.011 (2H, d
like, J=11.6 Hz), 3.224 (2H, t like, J=6.0 Hz)
5.800 (1H, dd, J=1.8, 6.2 Hz), 5.75-6.85 (1H, m),
6.59-6.72 (3H, m), 6.94-7.00 (2H, m), 7.064 (1H,
s), 7.23-7.26 (1H ,m).

25 2) The procedure of Example 67-2) was generally
followed to provide N-[1-[2-(thiophen-3-yl)ethan-1-
yl]piperidin-4-ylmethyl]-5-thia-1,8b-
diazaacenaphthylene-4-carboxamide dihydrochloride as
orange-colored crystals.

30 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40-1.90 (5H, m), 2.78-
2.95 (2H, m), 3.00-3.18 (4H, m), 3.18-3.35 (2H,
m), 3.48-3.60 (2H, m), 6.576 (1H, d, J=7.4 Hz),
6.953 (1H, d, J=8.4 Hz), 7.056 (1H, dd, J=1.2, 5.0
Hz), 7.17-7.32 (3H, m), 7.52-7.56 (1H, m), 7.621
(1H, s), 8.87-8.93 (1H, m), 10.53 (1H, br s).

35 IR (KBr): 3430, 3250, 3050, 2930, 2680, 1635, 1565,
1540, 1500, 1440, 1390, 1290, 1280, 1220, 780 cm⁻¹.

Elemental analysis for $C_{22}H_{26}N_4OS_2Cl_2 \cdot 0.5H_2O$

Calcd.: C, 52.17; H, 5.37; N, 11.06

Found : C, 52.52; H, 5.16; N, 10.98

Example 97

5 **Synthesis of N-[1-[2-(furan-3-yl)ethan-1-yl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride**

10 1) The procedure of Example 67-1) was generally followed to provide N-[1-[2-(furan-3-yl)ethan-1-yl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red oil.

15 1H -NMR (200 MHz, CDCl₃) δ: 1.23-1.40 (2H, m), 1.43-1.60 (1H, m), 1.62-1.78 (2H, m), 1.985 (2H, J=1.6, 11.6 Hz), 2.48-2.66 (4H, m), 2.991 (2H, d like, J=11.4 Hz), 3.216 (2H, t, J=6.1 Hz), 5.792 (1H, dd, J=1.7, 6.1 Hz), 5.78-5.90 (1H, m), 6.284 (1H, s), 6.58-6.72 (3H, m), 7.052 (1H, s), 7.255 (1H, s), 7.347 (1H, t, J=1.6 Hz).

20 2) The procedure of Example 67-2) was generally followed to provide N-[1-[2-(furan-3-yl)ethan-1-yl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

25 1H -NMR (200 MHz, DMSO-d₆) δ: 1.45-1.90 (5H, m), 2.80-2.95 (4H, m), 3.00-3.10 (2H, m), 3.15-3.30 (2H, m), 3.43-3.60 (2H, m), 6.42-6.45 (1H, m), 6.590 (1H, d, J=7.2 Hz), 6.964 (1H, d, J=8.8 Hz), 7.19-7.31 (2H, m), 7.56-7.64 (3H, m), 8.85-9.00 (1H, m), 10.6 (1H, br s).

30 IR (KBr): 3420, 3250, 3070, 3000, 2940, 2680, 2640, 1635, 1585, 1540, 1500, 1470, 1440, 1395, 1310, 1300, 1280, 1220, 1160, 1020, 940, 875, 800, 780, 630, 600 cm⁻¹.

Elemental analysis for $C_{22}H_{26}N_4O_2SCl_2 \cdot 1.0H_2O$

35 Calcd.: C, 52.91; H, 5.65; N, 11.22

Found : C, 53.27; H, 5.38; N, 11.22

Example 98

Synthesis of N-[1-[(thiazol-4-yl)methyl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride

- 5 1) Synthesis of N-[1-[(thiazol-4-yl)methyl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a solution of 255 mg (1.5 mM) of 4-chloromethylthiazole, 387 mg (1 mM) of N-(piperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride, and 697 ml (5 mM) of triethylamine in ethanol (10 ml) was added 225 mg (1.5 mM) of sodium iodide at room temperature and the mixture was refluxed on an oil bath at 90°C overnight. To this reaction mixture was added water and the reaction product was extracted into ethyl acetate. The organic layer was washed with water and saturated aqueous solution of sodium chloride and dried over Na₂SO₄. The solvent was then distilled off under reduced pressure and the residue was subjected to silica gel column chromatography. The fractions eluting with ethyl acetate/ethanol/triethylamine (20/20/1) were pooled to provide the title compound as red oil (150 mg).

¹H-NMR (200 MHz, CDCl₃) δ: 1.25-1.45 (2H, m), 1.45-1.60 (1H, m), 1.60-1.72 (2H, m), 2.049 (2H, t like, J=11.4 Hz), 2.966 (2H, d like, J=11.8 Hz), 3.206 (2H, t like, J=6.0 Hz), 3.722 (2H, s), 5.791 (1H, dd, J=1.8, 6.2 Hz), 5.75-5.90 (1H, m), 6.59-6.71 (3H, m), 7.050 (1H, s), 7.184 (1H, d, J=2.2 Hz), 8.786 (1H, d, J=2.0 Hz).

- 20 2) Synthesis of N-[1-[(thiazol-4-yl)methyl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride

To a solution of N-[1-[(thiazol-4-yl)methyl]-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol was added 2 ml (8.0 mM) of 4N-HCl/ethyl acetate. The solvent was distilled off under

reduced pressure and the residue was diluted with ether. The crystals that formed were harvested by filtration and rinsed with ethanol and diethyl ether to provide the title compound as orange-colored crystals
5 (150 mg, 28%).

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.35-1.90 (5H, m), 2.80-
3.25 (4H, m), 3.30-3.45 (2H, m), 4.431 (2H, d,
J=4.6 Hz), 6.674 (1H, d, J=6.8 Hz), 7.010 (1H, d,
J=9.2 Hz), 7.21-7.38 (2H, m), 7.707 (1H, s), 8.052
10 (1H, d, J=1.8 Hz), 8.90-9.10 (1H, m), 9.232 (1H,
d, J=2.0 Hz), 10.6 (1H, br s).

IR (KBr): 3400, 2950, 1635, 1560, 1540, 1500, 1290,
1220, 1110, 940, 890, 820, 780 cm⁻¹.

Elemental analysis for C₂₀H₂₄N₃OS₂Cl₃•0.5H₂O

15 Calcd.: C, 45.33; H, 4.75; N, 13.22
Found : C, 45.31; H, 5.07; N, 13.09

Example 99

Synthesis of N-[1-(3-cyclohexylpropan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride
20

1) The procedure of Example 67-1) was generally followed to provide N-[1-(3-cyclohexylpropan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple
25 amorphous substance.

¹H-NMR (200 MHz, CDCl₃) δ: 0.75-1.87 (m, 20H), 2.30 (t,
J=11.0 Hz, 2H), 2.53-2.62 (m, 2H), 3.13-3.25 (m,
4H), 5.75 (dd, J=2.6, 5.4 Hz, 1H), 6.52-6.64 (m,
2H), 6.90 (s, 1H), 7.02 (m, 2H).

30 2) The procedure of Example 67-2) was generally followed to provide N-[1-(3-cyclohexylpropan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

35 ¹H-NMR (200 MHz, DMSO-d₆) δ: 0.75-1.82 (m, 20H), 2.63-
3.48 (m, 8H), 6.60 (d, J=7.2 Hz, 1H), 6.97 (d,

J=8.6 Hz, 1H), 7.19-7.31 (m, 2H), 7.64 (s, 1H),
8.85-8.94 (m, 1H).

IR (KBr): 3438, 2924, 1635, 1535, 1298, 788 cm⁻¹.

Elemental analysis for C₂₅H₃₆N₄OSCl₂•2.1H₂O

5 Calcd.: C, 54.65; H, 7.38; N, 10.20

Found : C, 54.41; H, 7.37; N, 10.11

Example 100

Synthesis of N-[1-[(quinolin-2-yl)methyl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride

10 1) The procedure of Example 98-1) was generally followed to provide N-[1-[(quinolin-2-yl)methyl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red oil.

15 ¹H-NMR (200 MHz, CDCl₃) δ: 1.23-1.44 (2H, m), 1.45-1.72 (3H, m), 2.128 (2H, t like J=11.5 Hz), 2.940 (2H, d like, J=11.6 Hz), 3.222 (2H, t like, J=6.0 Hz), 3.823 (2H, s), 5.781 (1H, dd, J=1.8, 6.2 Hz), 5.78-5.90 (1H, m), 6.57-6.70 (3H, m), 7.037 (1H, s), 7.47-7.82 (4H, m), 8.05-8.14 (2H, m).

20 2) The procedure of Example 98-2) was generally followed to provide N-[1-[(quinolin-2-yl)methyl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride as orange-colored crystals.

25 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.45-1.90 (5H, m), 3.00-3.25 (4H, m), 3.45-3.60 (2H, m), 4.654 (2H, br s), 6.672 (1H, d, J=6.8 Hz), 7.008 (1H, d, J=9.0 Hz), 7.245 (1H, s), 7.336 (1H, dd, J=7.6, 9.1 Hz), 30 7.16-7.22 (2H, m), 7.80-7.88 (2H, m), 8.02-8.12 (2H, m), 8.523 (1H, d, J=8.4 Hz), 8.98-9.05 (1H, m), 10.6 (1H, br s).

IR (KBr): 3420, 2620, 1630, 1550, 1530, 1500, 1390, 1300, 1210, 940, 790 cm⁻¹.

35 Elemental analysis for C₂₆H₂₈N₅OSCl₃•2.0H₂O

Calcd.: C, 51.96; H, 5.37; N, 11.65

Found : C, 52.12; H, 5.47; N, 11.81

Example 101

Synthesis of N-[1-[3-(4-pyridyl)propan-1-yl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-

5 carboxamide trihydrochloride

1) The procedure of Example 98-1) was generally followed to provide N-[1-[3-(4-pyridyl)propan-1-yl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red oil.

10 $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ: 1.23-1.38 (2H, m), 1.42-1.60 (1H, m), 1.60-1.78 (2H, m), 1.80-1.98 (3H, m), 2.05-2.13 (1H, m), 2.341 (2H, t like $J=7.5$ Hz), 2.627 (2H, t, $J=7.7$ Hz), 2.911 (2H, d like, $J=11.8$ Hz), 3.200 (2H, t, $J=6.2$ Hz), 5.783 (1H, dd, $J=2.0$, 6.2 Hz), 5.92-6.05 (1H, m), 6.58-6.69 (3H, m), 7.030 (1H, s), 7.114 (2H, dd, $J=1.4$, 4.8 Hz), 8.481 (2H, dd, $J=1.4$, 4.4 Hz).

15 2) The procedure of Example 98-2) was generally followed to provide N-[1-[3-(4-pyridyl)propan-1-yl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride as orange-colored crystals.

20 $^1\text{H-NMR}$ (200 MHz, DMSO-d_6) δ: 1.45-1.90 (5H, m), 2.08-2.20 (2H, m), 2.70-3.28 (8H, m), 3.471 (2H, d like), 6.530 (1H, d, $J=7.2$ Hz), 6.928 (1H, d, $J=9.0$ Hz), 7.12-7.25 (2H, m), 7.575 (1H, s), 7.944 (2H, d, $J=5.8$ Hz), 8.851 (2H, d, $J=5.4$ Hz), 8.80-8.91 (1H, m), 10.6 (1H, br s).

25 IR (KBr): 3420, 2920, 2700, 1635, 1500, 1295, 1220, 790, 780 cm^{-1} .

30 Elemental analysis for $\text{C}_{24}\text{H}_{30}\text{N}_5\text{OSCl}_3 \cdot 1.5\text{H}_2\text{O}$

Calcd.: C, 50.57; H, 5.84; N, 12.29

Found : C, 50.59; H, 5.89; N, 12.10

Example 102

35 Synthesis of N-[1-(2-(3-indolyl)ethan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

dihydrochloride

1) The procedure of Example 67-1) was generally followed to provide N-[1-(2-(3-indolyl)ethan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-

5 diazaacenaphthylene-4-carboxamide as deep-red amorphous substance.

¹H-NMR (200 MHz, CDCl₃) δ: 1.20-1.45 (2H, m), 1.45-1.90 (3H, m), 1.95-2.15 (2H, m), 2.60-2.80 (2H, m), 2.90-3.15 (4H, m), 3.23 (2H, t, J=6.0 Hz), 5.79 (1H, dd, J=1.7, 6.1 Hz), 5.91 (1H, br t, J=6.1 Hz), 6.58-6.75 (3H, m), 7.00-7.25 (4H, m), 7.36 (1H, d, J=7.2 Hz), 7.62 (1H, d, J=7.2 Hz), 8.14 (1H, br s).

IR (KBr): 3334, 2922, 1618, 1541, 1510, 1481, 1456, 1342, 1281, 1153, 744 cm⁻¹.

15 2) The procedure of Example 67-2) was generally followed to provide N-[1-(2-(3-indolyl)ethan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as

20 orange-colored crystals.

¹H-NMR (200 MHz, CD₃OD) δ: 1.40-1.70 (2H, m), 1.70-2.10 (3H, m), 2.90-3.15 (2H, m), 3.15-3.50 (6H, m), 3.60-3.80 (2H, m), 6.59 (1H, d, J=7.8 Hz), 6.95-7.23 (5H, m), 7.34-7.41 (2H, m), 7.51 (1H, s), 7.61 (1H, d, J=7.0 Hz).

IR (KBr): 3392, 3062, 2935, 2727, 1633, 1564, 1539, 1504, 1456, 1292, 1216, 1105, 748 cm⁻¹.

Elemental analysis for C₂₆H₂₉N₅OSCl₂•2.0H₂O

Calcd.: C, 55.12; H, 5.87; N, 12.36
30 Found : C, 55.16; H, 6.03; N, 12.01

Example 103

Synthesis of N-(1-benzylpiperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-(1-benzylpiperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a solution of 0.58 g (1.5 mM) of N-(piperidin-

4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride and 1.0 ml (7.5 mM) of triethylamine in ethanol was added 0.19 ml (1.6 mM) of benzyl bromide at room temperature, and the mixture was
5 refluxed under nitrogen for 6 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with methylene chloride. The organic layer was washed with saturated aqueous solution of sodium chloride and dried
10 over MgSO₄. The resulting crude product was purified by column chromatography (methanol/ethyl acetate 40%) to provide the title compound.

Yield 479 mg (79%)

15 ¹H-NMR (200 MHz, CDCl₃) δ: 1.17-1.69 (m, 5H), 1.94 (t, J=11.0 Hz, 2H), 2.88 (br d, J=11.6 Hz, 2H), 3.17 (t, J=5.9 Hz, 2H), 3.48 (s, 2H), 5.72-5.76 (m, 1H), 6.35-6.50 (m, 1H), 6.59-6.64 (m, 3H), 6.96-6.97 (m, 1H), 7.18-7.38 (m, 5H).

20 2) Synthesis of N-(1-benzylpiperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

In a solution of 479 mg (1.18 mmol) of N-(1-benzylpiperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (4 ml) was
25 added 1.0 ml (4 mM) of 4N-HCl/methnol and the mixture was stirred at room temperature for several minutes. The solvent was then distilled off under reduced pressure and the residue was diluted with ethanol and diethyl ether. The resulting crystals were collected
30 by filtration and rinsed with ethanol and diethyl ether to provide the title compound.

Orange-colored crystals. Yield 424 mg (73%)

35 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.42-1.87 (m, 5H), 2.79-3.35 (m, 6H), 4.25 (br s, 2H), 6.59 (d, J=7.2 Hz, 1H), 6.96 (d, J=9.0 Hz, 1H), 7.17-7.30 (m, 2H), 7.44-7.47 (m, 3H), 7.59-7.65 (m, 3H), 8.83-8.89

(m, 1H).

Elemental analysis for C₂₃H₂₆N₄OSCl₂•1.0H₂O

Calcd.: C, 55.76; H, 5.70; N, 11.31

Found : C, 55.71; H, 5.70; N, 11.57

5 Example 104

Synthesis of N-(1-phenethylpiperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

10 1) The procedure of Example 103-1) was generally followed to provide N-(1-phenethylpiperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

15 ¹H-NMR (200 MHz, CDCl₃) δ: 1.23-2.10 (m, 5H), 2.01 (t, J=11.3 Hz, 2H), 2.54-2.62 (m, 2H), 2.77-2.85 (m, 2H), 3.02 (br d, J=11.2 Hz, 2H), 3.22 (t, J=5.3 Hz, 2H), 5.76-5.81 (m, 1H), 5.92-6.13 (m, 1H), 6.56-6.69 (m, 3H), 7.02-7.05 (s, 1H), 7.16-7.32 (m, 5H).

20 2) The procedure of Example 103-2) was generally followed to provide N-(1-phenethylpiperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

25 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40-1.87 (m, 7H), 2.79-3.59 (m, 8H), 6.55 (d, J=7.0 Hz, 1H), 6.94 (d, J=9.2 Hz, 1H), 7.15-7.39 (m, 7H), 7.60 (s, 1H), 8.80-8.91 (m, 1H).

IR (KBr): 3415, 3057, 2941, 2702, 1637, 1535, 1294, 1215, 789 cm⁻¹.

Elemental analysis for C₂₄H₂₈N₄OSCl₂•0.5H₂O

Calcd.: C, 57.60; H, 5.84; N, 11.19

30 Found : C, 57.52; H, 5.75; N, 11.00

Example 105

Synthesis of N-[1-(4-phenylbutan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

35 1) The procedure of Example 103-1) was generally followed to provide N-[1-(4-phenylbutan-1-yl)piperidin-

4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

5 ¹H-NMR (200 MHz, CDCl₃) δ: 1.18-1.94 (m, 11H), 2.32 (t, J=7.4 Hz, 2H), 2.62 (t, J=7.2 Hz, 2H), 2.91 (br d, J=11.2 Hz, 2H), 3.20 (t, J=6.2 Hz, 2H), 5.79 (dd, J=1.6, 6.2 Hz, 1H), 5.75-5.90 (m, 1H), 6.56-6.70 (m, 3H), 7.04-7.30 (m, 6H).

10 2) The procedure of Example 103-2) was generally followed to provide N-[1-(4-phenylbutan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

15 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.30-1.85 (m, 9H), 2.53-3.20 (m, 10H), 6.53 (d, J=7.6 Hz, 1H), 6.93 (d, J=9.2 Hz, 1H), 7.11-7.32 (m, 7H), 7.57 (s, 1H), 8.75-8.86 (m, 1H).

IR (KBr): 1635, 1566, 1533, 1502, 1294, 1217, 787 cm⁻¹.

Elemental analysis for C₂₆H₃₂N₄OSCl₂•2.1H₂O

Calcd.: C, 56.03; H, 6.55; N, 10.05

Found : C, 55.78; H, 6.55; N, 10.05

20 Example 106

Synthesis of N-[1-(5-phenylpentan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

25 1) The procedure of Example 103-1) was generally followed to provide N-[1-(5-phenylbutan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

30 ¹H-NMR (200 MHz, CDCl₃) δ: 1.25-1.90 (m, 10H), 2.34-3.31 (m, 11H), 5.74 (dd, J=2.2, 5.8 Hz, 1H), 6.51-6.63 (m, 2H), 6.90-7.31 (m, 7H).

IR (KBr): 3440, 1628, 1551, 1281, 1151 cm⁻¹.

35 2) The procedure of Example 103-2) was generally followed to provide N-[1-(5-phenylbutan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.25-1.85 (m, 11H), 2.65-

3.20 (m, 10H), 2.59 (t, J=7.5 Hz, 2H), 6.55 (d, J=8.0 Hz, 1H), 6.95 (d, J=8.8 Hz, 1H), 7.13-7.32 (m, 7H), 7.60 (s, 1H), 8.75-8.86 (m, 1H).

IR(KBr): 1635, 1566, 1535, 1500, 1444, 1294, 1217 cm⁻¹.

5 Elemental analysis for C₂₇H₃₄N₄OSCl₂•1.8H₂O

Calcd.: C, 57.30; H, 6.70; N, 9.90

Found : C, 57.51; H, 9.96; N, 9.96

Example 107

10 Synthesis of N-[1-(3-phenyl-2-propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[1-(3-phenyl-2-propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

15 To a solution of 0.58 g (1.5 mM) of N-(piperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride and 1.0 ml (7.2 mM) of triethylamine in ethanol (6 ml) was added 0.355 g (1.8 mM) of cinnamyl bromide at room temperature and the 20 mixture was refluxed under nitrogen for 24 hours. To this reaction mixture was further added 0.29 g (1.47 mM) of cinnamyl bromide and the mixture was refluxed for 2 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water 25 and extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The resulting crude product was purified by column chromatography (methanol-chloroform = 1:19-1:10-1:5) to provide the 30 title compound.

Red-purple amorphous substance. Yield 379 mg (59%)

¹H-NMR (200 MHz, CDCl₃) δ: 1.27-1.80 (m, 5H), 2.03 (br t, J=10.9 Hz, 2H), 2.90-3.25 (m, 6H), 5.75 (dd, J=2.5, 5.3 Hz, 1H), 6.28 (dt, J=6.7, 15.8 Hz, 1H), 35 6.49-6.65 (m, 4H), 6.69 (s, 1H), 6.99 (s, 1H), 7.23-7.41 (m, 5H).

2) Synthesis of N-[1-(3-phenyl-2-propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 0.3919 g (0.84 mM) of N-[1-(3-phenyl-2-propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (4 ml) was added 1.0 ml (4 mM) of 4N-HCl/methanol. The solvent was distilled off under reduced pressure and the residue was diluted with ethanol and diethyl ether.

10 The resulting crystals were collected by filtration and rinsed with ethanol and diethyl ether to provide the title compound.

Orange-colored crystals. Yield 330.2 mg (77%)

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.38-1.91 (m, 5H), 2.81-3.10 (m, 4H), 3.41-3.53 (m, 2H), 3.84 (br d, J=6.8 Hz, 2H), 6.32-6.49 (m, 1H), 6.57 (d, J=7.2 Hz, 1H), 6.82 (d, J=16 Hz, 1H), 6.95 (d, J=8.8 Hz, 1H), 7.15-7.53 (m, 7H), 7.61 (s, 1H), 8.80-8.93 (m, 1H).

20 IR (KBr): 3452, 1639, 1292, 1215 cm⁻¹.

Elemental analysis for C₂₅H₂₈N₄OSCl₂•0.5H₂O

Calcd.: C, 58.59; H, 5.70; N, 10.93

Found : C, 58.37; H, 5.84; N, 10.66

Example 108

25 Synthesis of N-[1-(2-phenoxyethan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[1-(2-phenoxyethan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

30 Under nitrogen gas, 0.37 ml (4.78 mM) of methanesulfonyl chloride was added to a solution of 0.44 g (3.18 mM) of phenoxyethanol and 0.89 ml (6.39 mM) of triethylamine in methylene chloride (6 ml) at 0°C and the mixture was stirred at the prevailing temperature
35 for 35 minutes. The reaction was stopped by adding saturated aqueous solution of sodium hydrogen carbonate

and the reaction mixture was extracted with diethyl ether. The organic layer was washed serially with water and saturated aqueous solution of sodium chloride and dried over $MgSO_4$. The solvent was then distilled off under reduced pressure to provide 0.6989 g (<3.18 mM) of phenoxyethyl mesylate. To a solution of 0.58 g (1.5 mM) of N-(piperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride and 1.0 ml (7.2 mM) of triethylamine in ethanol (6.0 ml) was added 0.6989 g (<3.18 mM) of the above phenoxyethyl mesylate at room temperature and the mixture was refluxed under nitrogen for 17 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over $MgSO_4$. The resulting crude product was purified by column chromatography (methanol/ethyl acetate 30-40%) to provide the title compound.

Red-purple amorphous substance. Yield 414 mg (63%).
 1H -NMR (200 MHz, $CDCl_3$) δ : 1.21-2.18 (m, 7H), 2.80 (t, J=5.9 Hz, 2H), 3.02 (br d, J=11.6 Hz, 2H), 3.20 (t, J=6.1 Hz, 2H), 4.10 (t, J=5.9 Hz, 2H), 5.78 (dd, J=2.0, 6.0 Hz, 1H), 6.01 (br t, J=5.8 Hz, 1H), 6.57-6.70 (m, 3H), 6.86-6.98 (m, 3H), 7.03 (s, 1H), 7.24-7.32 (m, 2H).

2) Synthesis of N-[1-(2-phenoxyethan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a suspension of 414 mg (0.95 mM) of N-[1-(2-phenoxyethan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (9 ml) was added 1.0 ml (4 mM) of 4N-HCl/methanol and the mixture was stirred at room temperature for 30 minutes. The resulting crystals were collected by filtration and rinsed with ethanol and ether to provide the title

compound.

Orange-colored crystals. Yield 363 mg (70%)

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.41-1.90 (m, 5H), 2.93-3.60 (m, 8H), 4.36-4.45 (m, 2H), 6.60 (d, J=6.8 Hz, 1H), 6.94-7.02 (m, 4H), 7.21-7.37 (m, 4H), 7.64 (s, 1H), 8.91-8.97 (m, 1H).

IR (KBr): 3388, 3238, 3057, 2638, 2514, 1639, 1294, 1230, 797, 764 cm⁻¹.

Elemental analysis for C₂₄H₂₈N₄O₂SCl₂•0.5H₂O

Calcd.: C, 55.81; H, 5.66; N, 10.85
Found : C, 55.84; H, 5.69; N, 10.69

Example 109

Synthesis of N-[1-(4-phenoxybutan-1-yl)piperidin-4-yl-methyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

dihydrochloride

1) Synthesis of N-[1-(4-phenoxybutan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a solution of 0.58 g (1.5 mM) of N-(piperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-

carboxamide dihydrochloride and 1.0 ml (27.5 mM) of triethylamine in ethanol (6 ml) was added 0.45 g (1.96 mM) of 4-phenoxybutyl bromide at room temperature and the mixture was refluxed under nitrogen for 14 hours.

To this reaction mixture was further added 0.23 g (1.0 mM) of 4-phenoxybutyl bromide and the mixture was refluxed for 6 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The resulting crude product was purified by column chromatography (methanol/chloroform = 1/15-1/10-1/5) to provide the title compound.

Red-purple amorphous substance. Yield 324 mg (47%)

¹H-NMR (200 MHz, CDCl₃) δ: 1.40-1.92 (m, 9H), 2.15-2.28 (m, 2H), 2.53-2.67 (m, 2H), 3.12-3.22 (m, 4H),

3.97 (br t, J=5.3 Hz, 2H), 5.74 (dd, J=2.4, 5.6 Hz, 1H), 6.58-6.61 (m, 2H), 6.65-6.76 (m, 1H), 6.81-6.97 (m, 3H), 7.02 (s, 1H), 7.23-7.31 (m, 3H).

5 2) **Synthesis of N-[1-(4-phenoxybutan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride**

To a solution of 0.3241 g (0.70 mM) of N-[1-(4-phenoxybutan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (4 ml) was added 1.0 ml (4 mM) of 4N-HCl/methanol. The solvent was distilled off under reduced pressure and the residue was diluted with ethanol and ether. The resulting crystals were collected by filtration and rinsed with ethanol and diethyl ether to provide the title compound.

Orange-colored crystals. Yield 270 mg (70%)

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.35-1.93 (m, 9H), 2.65-3.21 (m, 6H), 3.43-3.49 (m, 2H), 3.99 (t, J=5.6 Hz, 2H), 6.58 (d, J=7.4 Hz, 1H), 6.89-6.98 (m, 4H), 7.19-7.33 (m, 4H), 7.63 (s, 1H), 8.89-8.94 (m, 1H).

IR (KBr): 3435, 3051, 2943, 1635, 1294, 1241, 764 cm⁻¹.

Elemental analysis for C₂₆H₃₂N₄O₂SCl₂•1.0H₂O

25 Calcd.: C, 56.41; H, 6.19; N, 10.12
 Found : C, 56.57; H, 6.07; N, 10.19

Example 110

30 **Synthesis of N-[1-(3-phenoxypropan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride**

1) The procedure of Example 109-1) was generally followed to provide N-[1-(3-phenoxypropan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

¹H-NMR (200 MHz, CDCl₃) δ: 1.20-1.73 (m, 5H), 1.90-2.08

(m, 4H), 2.50-2.57 (m, 2H), 2.98 (br d, J=11.2 Hz, 2H), 3.18 (t, J=6.1 Hz, 2H), 3.99 (t, J=6.2 Hz, 2H), 5.74 (dd, J=3.0, 5.0 Hz, 1H), 6.52-6.68 (m, 4H), 6.82-6.97 (m, 4H), 7.17-7.32 (m, 2H).

5 2) The procedure of Example 109-2) was generally followed to provide N-[1-(3-phenoxypropan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

10 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.42-1.95 (m, 5H), 2.10-2.28 (m, 2H), 2.81-3.29 (m, 6H), 3.43-3.56 (m, 2H), 4.05 (t, J=6.0 Hz, 2H), 6.61 (d, J=7.4 Hz, 1H), 6.91-6.9 (m, 4H), 7.21-7.34 (m, 4H), 7.65 (s, 1H), 8.87-9.00 (m, 1H).

15 IR (KBr): 3421, 3236, 3049, 2941, 2642, 2532, 1635, 1295, 1294, 1240, 762 cm⁻¹.

Elemental analysis for C₂₅H₃₀N₄O₂SCl₂•0.5H₂O

Calcd.: C, 56.60; H, 5.89; N, 10.56

Found : C, 56.38; H, 5.79; N, 10.56

20 Example 111

Synthesis of N-[1-(3-(2-fluorophenoxy)propan-1-yl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[1-(3-(2-fluorophenoxy)propan-1-yl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a solution of 0.58 g (1.5 mM) of N-(piperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride and 1.0 ml (7.5 mM) of triethylamine in ethanol were added 0.37 g (2.0 mM) of 3-(2-fluorophenoxy)-propyl chloride and 0.28 g (1.9 mM) of sodium iodide at room temperature and the mixture was refluxed under nitrogen for 20 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with chloroform. The organic layer was washed with

saturated aqueous solution of sodium chloride and dried over MgSO₄. The resulting crude product was purified by column chromatography (methanol/ethyl acetate 30-50%) to provide the title compound.

5 Red-purple amorphous substance. Yield 244 mg (35%)
¹H-NMR (200 MHz, CDCl₃) δ: 1.16-2.06 (m, 9H), 2.48-2.55
(m, 2H), 2.94 (br d, J=11.6 Hz, 2H), 3.19 (t,
J=6.2 Hz, 2H), 4.07 (t, J=6.4 Hz, 2H), 5.77 (dd,
J=2.5, 5.3 Hz, 1H), 6.25 (br t, J=5.8 Hz, 1H),
10 6.61-6.67 (m, 3H), 6.84-7.14 (m, 5H).

10 2) Synthesis of N-[1-(3-(2-fluorophenoxy)propan-1-yl)-
piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-
4-carboxamide dihydrochloride

To a solution of 244 mg (0.52 mM) of N-[1-(3-(2-fluorophenoxy)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (4 ml) was added 1.0 ml (4.0 mM) of 4N-HCl/methanol. The solvent was distilled off under reduced pressure and the residue was purified by recrystallization to

20 provide the title compound.

Orange-colored crystals. Yield 218 mg (75%)
¹H-NMR (200 MHz, DMSO-d₆) δ: 1.35-1.90 (m, 5H), 2.13-
2.30 (m, 2H), 2.80-3.60 (m, 8H), 4.14 (t, J=5.8
Hz, 2H), 6.57 (d, J=7.4 Hz, 1H), 6.93-7.02 (m,
25 2H), 7.10-7.28 (m, 5H), 7.61 (s, 1H), 8.87 (m,
1H).

IR (KBr): 3429, 1635, 1506, 1290 cm⁻¹.

Elemental analysis for C₂₅H₂₉N₄O₂SCl₂F•1.0H₂O

Calcd.: C, 53.86; H, 5.60; N, 10.05
30 Found : C, 53.91; H, 5.46; N, 10.00

Example 112

Synthesis of N-[1-(3-(3-fluorophenoxy)propan-1-yl)-
piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-
4-carboxamide dihydrochloride

35 1) The procedure of Example 111-1) was generally
followed to provide N-[1-(3-(3-fluorophenoxy)propan-1-

yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

5 ¹H-NMR (200 MHz, CDCl₃) δ: 1.20-2.13 (m, 9H), 2.56 (br t, J=6.8 Hz, 2H), 3.00 (br d, J=11.0 Hz, 2H), 3.19 (t, J=5.7 Hz, 2H), 3.98 (t, J=6.0 Hz, 2H), 5.60-5.71 (m, 1H), 6.35-6.83 (m, 7H), 6.98-7.05 (m, 1H), 7.13-7.29 (m, 1H).

10 2) The procedure of Example 111-2) was generally followed to provide N-[1-(3-(3-fluorophenoxy)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

15 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.36-1.87 (m, 5H), 2.10-2.25 (m, 2H), 2.78-3.80 (m, 8H), 4.07 (t, J=5.9 Hz, 2H), 6.57 (d, J=6.8 Hz, 1H), 6.72-6.85 (m, 3H), 6.95 (d, J=9.0 Hz, 1H), 7.14-7.37 (m, 3H), 7.61 (s, 1H), 8.80-8.90 (m, 1H).
IR (KBr): 3413, 2948, 2648, 1635, 1491, 1288, 1136, 779 cm⁻¹.

Elemental analysis for C₂₅H₂₉N₄O₂SCl₂F•1.5H₂O

Calcd.: C, 53.00; H, 5.69; N, 9.89

Found : C, 53.01; H, 5.72; N, 9.65

Example 113

25 Synthesis of N-[1-(3-(4-fluorophenoxy)propan-1-yl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

30 1) The procedure of Example 111-1) was generally followed to provide N-[1-(3-(4-fluorophenoxy)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

35 ¹H-NMR (200 MHz, CDCl₃) δ: 1.25-2.13 (m, 7H), 2.55-2.62 (m, 2H), 3.00-3.06 (m, 4H), 3.19 (t, J=5.9 Hz, 2H), 3.96 (t, J=6.2 Hz, 2H), 5.75 (dd, J=3.0, 5.0 Hz, 1H), 6.58-6.65 (m, 3H), 6.72 (s, 1H), 6.77-

7.00 (m, 5H).

2) The procedure of Example 111-2) was generally followed to provide N-[1-(3-(4-fluorophenoxy)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-

5 diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40-2.22 (m, 7H), 2.77-3.54 (m, 8H), 4.03 (t, J=6.1 Hz, 2H), 6.54 (d, J=7.8 Hz, 1H), 6.89-7.24 (m, 7H), 7.58 (s, 1H), 8.78-8.86 (m, 1H).

10 IR (KBr): 3461, 3400, 2711, 1637, 1504, 1294, 1211, 835, 790 cm⁻¹.

Elemental analysis for C₂₅H₂₉N₄O₂SCl₂F•1.0H₂O

Calcd.: C, 53.86; H, 5.60; N, 10.05

15 Found : C, 53.65; H, 5.57; N, 9.81

Example 114

Synthesis of N-[1-(2-(2-fluorophenoxy)ethan-1-yl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

20 1) The procedure of Example 108-1) was generally followed to provide N-[1-(2-(2-fluorophenoxy)ethan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red oil.

¹H-NMR (200 MHz, CDCl₃) δ: 1.25-2.21 (7H, m), 2.847 (2H, t like, J=6.0 Hz), 3.00-3.10 (2H, d like), 3.217 (2H, t, J=6.0 Hz), 4.10-4.20 (2H, m), 5.799 (1H, dd, J=1.8, 6.2 Hz), 5.75-5.88 (1H, m), 6.60-6.73 (2H, m), 6.85-7.15 (6H, m).

2) The procedure of Example 108-2) was generally followed to provide N-[1-(2-(2-fluorophenoxy)ethan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40-1.95 (4H, m), 2.90-3.35 (5H, m), 3.40-3.65 (4H, m), 4.45-4.55 (2H, m), 6.645 (1H, d, J=7.6 Hz), 6.95-7.08 (2H, m),

7.13-7.35 (5H, m), 7.678 (1H, s), 8.85-8.98 (1H, m), 10.70 (1H, br s).

IR (KBr): 3420, 3050, 2950, 1635, 1560, 1535, 1280, 1260, 1220, 1150, 780, 760 cm⁻¹.

5 Elemental analysis for C₂₄H₂₇N₄O₂SCl₂F•2.5H₂O

Calcd.: C, 50.53; H, 5.65; N, 9.82

Found : C, 50.81; H, 5.68; N, 9.65

Example 115

Synthesis of N-[1-(2-(3-fluorophenoxy)ethan-1-yl)-
10 piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-
4-carboxamide dihydrochloride

1) The procedure of Example 108-1) was generally
followed to provide N-[1-(2-(3-fluorophenoxy)ethan-1-
yl)piperidin-4-ylmethyl]-5-thia-1,8b-
15 diazaacenaphthylene-4-carboxamide as red oil.

¹H-NMR (200 MHz, CDCl₃) δ: 1.25-1.45 (2H, m), 1.45-1.63
(1H, m), 1.63-1.78 (2H, m), 2.05-2.18 (2H, m),
2.798 (2H, t, J=6.0 Hz), 3.017 (2H, d like, J=11.8
Hz), 3.212 (2H, t, J=6.0 Hz), 4.080 (2H, t, J=5.7
Hz), 5.800 (1H, dd, J=1.8, 6.1 Hz), 5.75-5.90 (1H,
m), 6.58-6.73 (6H, m), 7.054 (1H, s), 7.16-7.27
(1H, m).

2) The procedure of Example 108-2) was generally
followed to provide N-[1-(2-(3-fluorophenoxy)ethan-1-
25 yl)piperidin-4-ylmethyl]-5-thia-1,8b-
diazaacenaphthylene-4-carboxamide dihydrochloride as
orange-colored crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.45-1.95 (4H, m), 2.92-
3.15 (4H, m), 3.18-3.35 (1H, m), 3.42-3.65 (4H,
m), 4.38-4.52 (2H, m), 6.603 (1H, d, J=7.2 Hz),
6.78-6.99 (4H, m), 7.20-7.42 (3H, m), 7.647 (1H,
s), 8.90-9.00 (1H, m), 10.70 (1H, br s).

IR (KBr): 3420, 3250, 3050, 2950, 1635, 1610, 1590,
1560, 1540, 1500, 1490, 1290, 1260, 1220, 1170,
35 1140, 780 cm⁻¹.

Elemental analysis for C₂₄H₂₇N₄O₂SCl₂F•1.0H₂O

Calcd.: C, 53.04; H, 5.38; N, 10.31

Found : C, 53.32; H, 5.59; N, 10.32

Example 116

Synthesis of N-[1-(2-(4-fluorophenoxy)ethan-1-yl)-
5 piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-
4-carboxamide dihydrochloride

1) The procedure of Example 108-1) was generally
followed to provide N-[1-(2-(4-fluorophenoxy)ethan-1-
yl)piperidin-4-ylmethyl]-5-thia-1,8b-
10 diazaacenaphthylene-4-carboxamide as red oil.

¹H-NMR (200 MHz, CDCl₃) δ: 1.20-1.42 (2H, m), 1.45-1.65
(1H, m), 1.63-1.77 (2H, m), 2.03-2.16 (2H, m),
2.783 (2H, t, J=5.9 Hz), 3.015 (2H, d like, J=11.8
Hz), 3.214 (2H, t, J=6.2 Hz), 4.055 (2H, t, J=5.9
Hz), 5.798 (1H, dd, J=1.6, 6.2 Hz), 5.75-5.85 (1H,
m), 6.59-6.72 (3H, m), 6.80-6.88 (2H, m), 6.89-
7.01 (2H, m), 7.058 (1H, s).

2) The procedure of Example 108-2) was generally
followed to provide N-[1-(2-(4-fluorophenoxy)ethan-1-
20 yl)piperidin-4-ylmethyl]-5-thia-1,8b-
diazaacenaphthylene-4-carboxamide dihydrochloride as
orange-colored crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40-1.90 (5H, m), 2.90-
3.15 (3H, m), 3.15-3.30 (1H, m), 3.40-3.60 (4H,
25 m), 4.33-4.42 (2H, m), 6.599 (1H, d, J=7.4 Hz),
6.94-7.06 (3H, m), 7.13-7.31 (4H, m), 7.644 (1H,
s), 8.85-8.95 (1H, m), 10.56 (1H, br s).

IR (KBr): 3420, 3250, 3050, 2950, 1635, 1560, 1540,
1500, 1290, 1250, 1210, 830, 780, 760 cm⁻¹.

30 Elemental analysis for C₂₄H₂₇N₄O₂SCl₂F•1.5H₂O

Calcd.: C, 52.17; H, 5.47; N, 10.14

Found : C, 52.28; H, 5.53; N, 10.06

Example 117

Synthesis of N-[1-(3-(2,4-difluorophenoxy)propan-1-yl)-
35 piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-
4-carboxamide dihydrochloride

1) The procedure of Example 111-1) was generally followed to provide N-[1-(3-(2,4-difluorophenoxy)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

5 ¹H-NMR (200 MHz, CDCl₃) δ: 1.21-1.73 (m, 4H), 1.90-2.08 (m, 5H), 2.54 (t, J=7.4 Hz, 2H), 2.96 (br d, J=12.2 Hz, 2H), 3.21 (t, J=6.2 Hz, 2H), 4.04 (t, J=6.3 Hz, 2H), 5.79 (dd, J=1.8, 6.2 Hz, 1H), 5.82-5.89 (m, 1H), 6.58-6.93 (m, 6H), 7.05 (s, 1H).

10 2) The procedure of Example 111-2) was generally followed to provide N-[1-(3-(2,4-difluorophenoxy)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

15 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.42-1.95 (m, 5H), 2.14-2.29 (m, 2H), 2.80-3.26 (m, 6H), 3.46-3.55 (m, 2H), 4.12 (t, J=5.9 Hz, 2H), 6.60 (d, J=7.2 Hz, 1H), 6.96 (d, J=8.8 Hz, 1H), 6.96-7.05 (m, 1H), 7.15-7.42 (m, 4H), 7.64 (s, 1H), 8.86-8.97 (m, 1H).

20 IR (KBr): 3460, 3381, 3246, 2951, 2702, 1639, 1510, 1294, 1215, 798 cm⁻¹.

Elemental analysis for C₂₅H₂₈N₄O₂SCl₂•1.0H₂O

25 Calcd.: C, 52.18; H, 5.25; N, 9.74
 Found : C, 52.31; H, 5.29; N, 9.67

Example 118

Synthesis of N-[1-(3-(4-chlorophenoxy)propan-1-yl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

30 1) The procedure of Example 111-1) was generally followed to provide N-[1-(3-(4-chlorophenoxy)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

35 ¹H-NMR (200 MHz, CDCl₃) δ: 1.19-2.01 (m, 9H), 2.50 (t,

5 J=7.5 Hz, 2H), 2.95 (br d, J=11.4 Hz, 2H), 3.20
 (t, J=6.2 Hz, 2H), 3.97 (t, J=6.4 Hz, 2H), 5.78
 (dd, J=2.2, 5.8 Hz, 1H), 6.07 (br t, J=5.9 Hz,
 1H), 6.63-6.68 (m, 3H), 6.80-6.85 (m, 2H), 7.02
 (s, 1H), 7.20-7.26 (m, 2H).

10 2) The procedure of Example 111-2) was generally
 followed to provide N-[1-(3-(4-chlorophenoxy)propan-1-
 yl)piperidin-4-ylmethyl]-5-thia-1,8b-
 diazaacenaphthylene-4-carboxamide dihydrochloride as
 orange-colored crystals.

15 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.39-1.90 (m, 5H), 2.10-
 2.26 (m, 2H), 2.76-3.31 (m, 6H), 3.43-3.58 (m,
 2H), 4.05 (t, J=6.0 Hz, 2H), 6.57 (d, J=7.4 Hz,
 1H), 6.92-7.01 (m, 3H), 7.16-7.37 (m, 4H), 7.61
 (s, 1H), 8.87 (m, 1H).

IR (KBr): 3404, 1635, 1495, 1292, 1242 cm⁻¹.

Elemental analysis for C₂₅H₂₉N₄O₂SCl₃•0.5H₂O

Calcd.: C, 53.15; H, 5.35; N, 9.92

Found : C, 53.40; H, 5.23; N, 9.92

20 Example 119

Synthesis of N-[1-(3-(2-methoxyphenoxy)propan-1-yl)-
piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-
4-carboxamide dihydrochloride

25 1) The procedure of Example 111-1) was generally
 followed to provide N-[1-(3-(2-methoxyphenoxy)propan-1-
 yl)piperidin-4-ylmethyl]-5-thia-1,8b-
 diazaacenaphthylene-4-carboxamide as red oil.

30 ¹H-NMR (200 MHz, CDCl₃) δ: 1.26-2.15 (9H, m), 2.630
 (2H, t, J=7.3 Hz), 3.02-3.08 (2H, m), 3.218 (2H,
 t, J=6.1 Hz), 3.861 (3H, s), 4.079 (2H, t, J=6.4
 Hz), 5.786 (1H, dd, J=1.8, 6.2 Hz), 5.90-6.05 (1H,
 m), 6.60-6.75 (3H, m), 6.907 (4H, s), 7.056 (1H,
 s).

35 2) The procedure of Example 111-2) was generally
 followed to provide N-[1-(3-(2-methoxyphenoxy)propan-1-
 yl)piperidin-4-ylmethyl]-5-thia-1,8b-

diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

5 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40-1.85 (5H, m), 2.10-2.30 (2H, m), 2.80-3.30 (6H, m), 3.45-3.60 (2H, m), 3.762 (3H, s), 4.00-4.06 (2H, m), 6.571 (1H, d, J=6.6 Hz), 6.86-7.01 (5H, m), 7.16-7.28 (2H, m), 7.611 (1H, s), 8.82-8.90 (1H, m).

10 IR (KBr): 3420, 2920, 1630, 1500, 1285, 1250, 1220, 1120, 780, 740 cm⁻¹.

10 Elemental analysis for C₂₆H₃₂N₄O₃SCl₂•1.5H₂O

Calcd.: C, 53.98; H, 6.10; N, 9.68

Found : C, 53.86; H, 6.14; N, 9.51

Example 120

15 Synthesis of N-[1-(3-(4-methoxyphenoxy)propan-1-yl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

20 1) The procedure of Example 111-1) was generally followed to provide N-[1-(3-(4-methoxyphenoxy)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

25 ¹H-NMR (200 MHz, CDCl₃) δ: 1.38-2.25 (m, 9H), 2.63-2.71 (m, 2H), 3.11 (br d, J=11.4 Hz, 2H), 3.17-3.26 (m, 2H), 3.77 (s, 3H), 3.97 (t, J=6.1 Hz, 2H), 5.77 (dd, J=2.0, 5.8 Hz, 1H), 6.15-6.27 (m, 1H), 6.60-6.67 (m, 2H), 6.77-6.83 (m, 5H), 7.05 (s, 1H).

30 2) The procedure of Example 111-2) was generally followed to provide N-[1-(3-(4-methoxyphenoxy)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

35 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40-1.95 (m, 5H), 2.11-2.24 (m, 2H), 2.78-3.30 (m, 6H), 3.43-3.53 (m, 2H), 3.70 (s, 3H), 3.98 (t, J=5.9 Hz, 2H), 6.56 (d, J=7.3 Hz, 1H), 6.87-6.97 (m, 5H), 7.15-7.28 (m, 2H), 7.61 (s, 1H), 8.80-8.92 (m, 1H).

IR (KBr): 3425, 3051, 2947, 2708, 2507, 1635, 1506,
1227 cm⁻¹.

Example 121

Synthesis of N-[1-(3-(4-tert-butylphenoxy)propan-1-yl)-
5-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-
4-carboxamide dihydrochloride

5 1) The procedure of Example 111-1) was generally
followed to provide N-[1-(3-(4-tert-
butylphenoxy)propan-1-yl)piperidin-4-ylmethyl]-5-thia-
10 1,8b-diazaacenaphthylene-4-carboxamide as red-purple
amorphous substance.

15 ¹H-NMR (200 MHz, CDCl₃) δ: 1.29 (s, 9H), 1.40-2.36 (m,
9H), 2.62-2.70 (m, 2H), 3.04-3.13 (m, 2H), 3.21
(t, J=6.2 Hz, 2H), 3.99 (t, J=6.0 Hz, 2H), 5.74
(dd, J=2.2, 5.8 Hz, 1H), 6.36-6.67 (m, 3H), 6.79-
6.84 (m, 2H), 6.90 (s, 1H), 7.05 (s, 1H), 7.26-
7.31 (m, 2H).

20 2) The procedure of Example 111-2) was generally
followed to provide N-[1-(3-(4-tert-
butylphenoxy)propan-1-yl)piperidin-4-ylmethyl]-5-thia-
1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride
as orange-colored solid.

25 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.25 (s, 9H), 1.35-1.92
(m, 5H), 2.06-2.23 (m, 2H), 2.80-3.56 (m, 8H),
4.02 (t, J=6.0 Hz, 2H), 6.56 (d, J=7.4 Hz, 1H),
6.83-6.89 (m, 2H), 6.94 (d, J=9.0 Hz, 1H), 7.10
(s, 1H), 7.19-7.32 (m, 3H), 7.60 (s, 1H), 8.72-
8.82 (m, 1H).

30 IR (KBr): 3429, 2954, 1635, 1510, 1294, 1244, 831, 785
cm⁻¹.

Example 122

Synthesis of N-[1-(3-(2,4,6-trimethylphenoxy)propan-1-
yl)piperidin-4-ylmethyl]-5-thia-1,8b-
diazaacenaphthylene-4-carboxamide dihydrochloride

35 1) The procedure of Example 111-1) was generally
followed to provide N-[1-(3-(2,4,6-

trimethylphenoxy)propan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

- 5 ¹H-NMR (200 MHz, CDCl₃) δ: 1.37-1.86 (m, 4H), 2.00-2.30
 (m, 5H), 2.21 (s, 9H), 2.75-2.83 (m, 2H), 3.12-
 3.19 (m, 4H), 3.76 (t, J=5.8 Hz, 2H), 5.69-5.73
 (m, 1H), 6.56-6.58 (m, 2H), 6.80 (s, 2H), 6.89 (s,
 1H), 6.99 (s, 1H), 7.14-7.29 (m, 1H).
- 10 2) The procedure of Example 111-2) was generally
 followed to provide N-[1-(3-(2,4,6-
 trimethylphenoxy)propan-1-yl)piperidin-4-ylmethyl]-5-
 thia-1,8b-diazaacenaphthylene-4-carboxamide
 dihydrochloride as orange-colored solid.
- 15 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40-1.95 (m, 4H), 2.05-
 2.40 (m, 3H), 2.17 (s, 9H), 2.80-3.36 (m, 6H),
 3.52 (br d, J=12.4 Hz, 2H), 3.74 (t, J=5.7 Hz,
 2H), 6.60 (d, J=7.0 Hz, 1H), 6.82 (s, 2H), 6.97
 (d, J=9.2 Hz, 1H), 7.20-7.31 (m, 2H), 7.65 (s,
 1H), 8.87-8.95 (m, 1H).
- 20 IR (KBr): 3392, 2947, 2715, 1635, 1492, 1294, 1215 cm⁻¹.

Example 123

- Synthesis of N-[1-[2-(phenylthio)ethan-1-yl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride
- 25 1) The procedure of Example 108-1) was generally
 followed to provide N-[1-[2-(phenylthio)ethan-1-
 yl]piperidin-4-ylmethyl]-5-thia-1,8b-
 diazaacenaphthylene-4-carboxamide as red solid.
- 30 ¹H-NMR (200 MHz, CDCl₃) δ: 1.20-1.40 (2H, m), 1.40-1.60
 (1H, m), 1.60-1.75 (2H, m), 1.92-2.08 (2H, m),
 2.58-2.66 (2H, m), 2.945 (2H, d like, J=11.2 Hz),
 3.02-3.10 (2H, m), 3.201 (2H, t, J=6.1 Hz), 5.791
 (1H, dd, J=1.7, 6.2 Hz), 6.58-6.71 (3H, m), 7.053
 (1H, s), 7.10-7.37 (5H, m).
- 35 2) The procedure of Example 108-2) was generally

followed to provide N-[1-[2-(phenylthio)ethan-1-yl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

5 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.30-1.90 (5H, m), 2.75-3.30 (7H, m), 3.38-3.60 (3H, m), 6.600 (1H, d, J=6.8 Hz), 6.966 (1H, d, J=9.2 Hz), 7.17-7.46 (7H, m), 7.641 (1H, s), 8.83-8.93 (1H, m), 10.84 (1H, br s).

10 IR (KBr): 3420, 3250, 3050, 2680, 1650, 1635, 1565, 1540, 1500, 1440, 1390, 1290, 1220, 750 cm⁻¹.

Elemental analysis for C₂₄H₂₈N₄OS₂Cl₂•0.5H₂O

Calcd.: C, 54.13; H, 5.49; N, 10.52

Found : C, 53.68; H, 5.83; N, 10.22

15 Example 124

Synthesis of N-[1-(phenylaminocarbonylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[1-

20 (phenylaminocarbonylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a solution of 581 mg (1.5 mM) of N-(piperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride and 759 mg (7.5 mM) of

25 triethylamine in ethanol (30 ml) was added 254 mg (1.5 mM) of chloroacetylaniline at room temperature, and the mixture was refluxed for 18 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with methylene chloride. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over Na₂SO₄. The resulting crude product was purified by column chromatography (methanol/ethyl acetate = 1/2) to provide the title compound as red oil.

35 ¹H-NMR (200 MHz, CDCl₃) δ: 1.25-1.45 (2H, m), 1.45-2.68 (1H, m), 1.70-1.80 (2H, m), 2.246 (2H, dt, J=2.2

11.65 Hz), 2.936 (2H, br d, J=11.8 Hz), 3.109 (2H, s), 3.248 (2H, t, J=6.4 Hz), 5.791 (1H, dd, J=1.6, 6.0 Hz), 5.88-5.95 (1H, m), 6.59-6.71 (3H, m), 7.05-7.15 (2H, m), 7.29-7.38 (2H, m), 7.52-7.58 (2H, m), 9.117 (1H, br s).

5 2) **Synthesis of N-[1-(phenylaminocarbonylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride**

10 To a solution of N-[1-(phenylaminocarbonylmethyl)-piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in chloroform-methanol (1:1) was added 2 ml (8.0 mM) of 4N-HCl/ethyl acetate. The solvent was distilled off under reduced pressure and the residue was diluted with ethanol/ether (1/10). The resulting crystals were collected by filtration and rinsed with ethanol and diethyl ether to provide the title compound as orange-colored crystals (506 mg, 60%).

15

20 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40-1.80 (5H, m), 3.00-3.30 (4H, m), 3.45-3.60 (2H, m), 4.152 (2H, s), 6.618 (1H, d, J=7.2 Hz), 6.977 (1H, d, J=8.8 Hz), 7.114 (1H, t, J=7.5 Hz), 7.24-7.39 (4H, m), 7.627 (1H, s), 7.666 (2H, s), 8.95-9.10 (1H, m), 10.00 (1H, br s), 11.016 (1H, s).

25 IR (KBr): 3400, 3250, 3050, 2950, 1690, 1630, 1600, 1560, 1540, 1500, 1440, 1390, 1300, 1210, 1110, 940, 780, 760 cm⁻¹.

Elemental analysis for C₂₄H₂₇N₅O₂SCl₂•2.5H₂O
Calcd.: C, 50.97; H, 5.70; N, 12.38
30 Found : C, 51.17; H, 5.68; N, 12.13

Example 125
Synthesis of N-[1-[(3,5-bis(trifluoromethyl)phenyl)amino-carbonylmethyl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride
35 1) **Synthesis of N-[1-[(3,5-bis(trifluoromethyl)phenyl)-**

aminocarbonylmethyl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a solution of 709 mg (3 mM) of 3,5-bis(trifluoromethyl)aniline and 455 mg (4.5 mM) of triethylamine in dichloromethane (20 ml) was added 386 mg (3.3 mM) of chloroacetyl chloride gradually with ice-cooling and the mixture was stirred at room temperature for 30 minutes. This reaction mixture was washed with 5% aqueous solution of sodium hydrogen carbonate and the organic layer was dried over Na_2SO_4 .
The solvent was then distilled off under reduced pressure to recover crystals (830 mg). This chloride was dissolved in ethanol (30 ml), followed by addition of 759 mg (7.5 mM) of triethylamine and 581 mg (1.5 mM) of N-(piperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride, and the mixture was refluxed at 90°C overnight. After removal of excess ethanol by concentration to about half the initial volume, the residue was diluted with water (20 ml) and extracted with dichloromethane. The organic layer was washed with water and dried and the solvent was distilled off. The residue was purified by silica gel column chromatography (methanol/ethyl acetate = 1/2) to provide the title compound as red oil (570 mg, 0.98 mM).

¹H-NMR (200 MHz, CDCl_3) δ : 1.33-1.49 (2H, m), 1.50-1.70 (1H, m), 1.73-1.85 (2H, m), 2.22-2.38 (2H, m), 2.85-3.00 (2H, m), 3.161 (2H, s), 3.282 (2H, t, J=6.4 Hz), 5.75-5.85 (2H, m), 6.60-6.73 (3H, m), 7.081 (1H, s), 7.616 (1H, s), 8.081 (2H, s), 9.458 (1H, br s).

2) Synthesis of N-[1-[(3,5-bis(trifluoromethyl)phenyl)-aminocarbonylmethyl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of N-[1-[(3,5-bis(trifluoromethyl)phenyl)aminocarbonylmethyl]piperidin-4-ylmethyl]-5-

5 thia-1,8b-diazaacenaphthylene-4-carboxamide in
chloroform-methanol (1:1) was added 2 ml (8.0 mM) of
4N-HCl/ethyl acetate. The solvent was distilled off
under reduced pressure and the residue was diluted with
ether. The resulting crystals were collected by
filtration and rinsed with ethanol and diethyl ether to
provide the title compound as orange-colored crystals
(404 mg, 41%).

10 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.45-1.95 (5H, m), 3.00-
3.40 (4H, m), 3.50-3.68 (2H, m), 4.268 (2H, s),
6.647 (1H, d, J=7.4 Hz), 6.996 (1H, d, J=9.2 Hz),
7.24-7.35 (2H, m), 7.698 (1H, s), 7.854 (1H, s),
8.392 (2H, s), 9.017 (1H, br s), 10.179 (1H, br
s), 12.225 (1H, s).
15 IR (KBr): 3420, 3230, 3050, 2950, 1700, 1635, 1560,
1540, 1500, 1470, 1440, 1380, 1280, 1215, 1180,
1130, 940, 890, 840, 780, 700, 680 cm⁻¹.

20 Elemental analysis for C₂₆H₂₅N₅O₂SCl₂F₆•0.2H₂O
Calcd.: C, 47.31; H, 3.88; N, 10.61
Found : C, 47.59; H, 4.19; N, 10.45

25 Example 126
Synthesis of N-[1-[(2,6-bis(trifluoromethyl)
phenyl)aminocarbonylmethyl]piperidin-4-ylmethyl]-5-
thia-1,8b-diazaacenaphthylene-4-carboxamide
dihydrochloride
1) The procedure of Example 125-1) was generally
followed to provide N-[1-[(2,6-
bis(trifluoromethyl)phenyl)amino-
carbonylmethyl]piperidin-4-ylmethyl]-5-thia-1,8b-
diazaacenaphthylene-4-carboxamide as red solid.
30 ¹H-NMR (200 MHz, CDCl₃) δ: 1.25-1.45 (2H, m), 1.55-1.85
(3H, m), 2.26-2.40 (2H, m), 2.88-2.90 (2H, m),
3.172 (2H, s), 3.266 (2H, t, J=6.1 Hz), 5.75-5.80
(1H, m), 5.809 (1H, dd, J=6.3, 1.8 Hz), 6.61-6.75
35 (3H, m), 7.075 (1H, s), 7.452 (1H, d like), 7.744
(1H, d like), 8.896 (1H, s), 10.20 (1H, br s).

2) The procedure of Example 125-2) was generally followed to provide N-[1-[(2,6-bis(trifluoromethyl)phenyl]amino-carbonylmethyl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as yellow crystals.

5 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40-1.70 (3H, m), 1.70-1.95 (3H, m), 3.00-3.20 (2H, m), 3.50-3.65 (2H, m), 4.15-4.40 (3H, m), 6.564 (1H, d, J=7.6 Hz), 6.950 (1H, d, J=9.2 Hz), 7.18-7.28 (2H, m), 7.616 (1H, s), 7.928 (1H, d-like), 8.85-9.00 (1H, m), 10.04 (1H, br s), 10.80 (1H, br s).
10 IR (KBr): 3400, 3230, 3050, 2950, 1700, 1630, 1580, 1560, 1540, 1500, 1430, 1390, 1330, 1315, 1600, 15
15 1210, 1180, 1130, 1080, 1040, 940, 840, 780, 740, 630 cm⁻¹.

Elemental analysis for C₂₆H₂₅N₅O₂SCl₂F₆•1.OH₂O

Calcd.: C, 46.30; H, 4.03; N, 10.38

Found : C, 46.16; H, 3.91; N, 10.40

20 Example 127

Synthesis of N-[1-[(4-fluorophenyl)aminocarbonylmethyl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

25 1) The procedure of Example 125-1) was generally followed to provide N-[1-[(4-fluorophenyl)aminocarbonylmethyl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red oil.

30 ¹H-NMR (200 MHz, CDCl₃) δ: 1.20-1.45 (2H, m), 1.50-1.70 (1H, m), 1.70-1.95 (2H, m), 2.18-2.35 (2H, m), 2.85-3.00 (2H, m), 3.107 (2H, s), 3.20-3.35 (2H, m), 5.797 (1H, dd, J=2.2, 5.5 Hz), 5.98-6.15 (1H, m), 6.59-6.77 (3H, m), 6.98-7.15 (3H, m), 7.45-7.65 (2H, m), 9.123 (1H, br s).

35 2) The procedure of Example 125-2) was generally

followed to provide N-[1-[(4-fluorophenyl)aminocarbonylmethyl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

5 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40-1.95 (6H, m), 2.98-3.30 (3H, m), 3.48-3.60 (2H, m), 4.157 (2H, s), 6.639 (1H, d, J=6.8 Hz), 6.990 (1H, d, J=9.2 Hz), 7.15-7.35 (3H, m), 7.63-7.75 (3H, m), 8.96-9.08 (1H, m), 10.026 (1H, br s), 11.162 (1H, s).

10 IR (KBr): 3400, 3230, 3050, 2950, 1695, 1630, 1560, 1535, 1500, 1300, 1210, 840, 780, 700, 620 cm⁻¹.

Elemental analysis for C₂₄H₂₆N₅O₂SCl₂F•2.2H₂O

Calcd.: C, 49.86; H, 5.30; N, 12.11

Found : C, 50.29; H, 5.31; N, 11.65

15 Example 128

Synthesis of N-[1-(benzylaminocarbonylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) The procedure of Example 125-1) was generally followed to provide N-[1-(benzylaminocarbonylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red oil.

20 ¹H-NMR (200 MHz, CDCl₃) δ: 1.05-1.30 (2H, m), 1.40-1.60 (1H, m), 1.655 (2H, br d like, J=12.8 Hz), 2.127 (2H, t like, J=10.7 Hz), 2.828 (2H, br d, J=11.4 Hz), 3.020 (2H, s), 3.152 (2H, t, J=6.4 Hz), 4.468 (2H, d, J=5.8 Hz), 5.741 (1H, dd, J=3.0, 5.2 Hz), 6.490 (1H, t, J=5.9 Hz), 6.59-6.65 (3H, m), 6.949 (1H, s), 7.239-7.385 (5H, m), 7.526-7.58 (1H, t, J=5.9 Hz).

25 2) The procedure of Example 125-2) was generally followed to provide N-[1-(benzylaminocarbonylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored crystals.

30 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40-1.90 (4H, m), 2.95-

3.51 (7H, m), 3.983 (2H, br s), 4.352 (2H, d,
J=5.8 Hz), 6.649 (1H, d, J=7.4 Hz), 7.003 (1H, d,
J=9.2 Hz), 7.20-7.39 (6H, m), 7.693 (1H, s), 9.05-
9.15 (1H, m), 9.316 (1H, t, J=5.9 Hz), 10.00 (1H,
br s).

5 IR (KBr): 3420, 3220, 3050, 2930, 1680, 1630, 1560,
1540, 1500, 1450, 1430, 1390, 1285, 1210, 1110,
950, 780, 740, 700 cm⁻¹.

Elemental analysis for C₂₅H₂₉N₅O₂SCl₂•0.5H₂O
10 Calcd.: C, 55.25; H, 5.56; N, 12.89
Found : C, 55.02; H, 6.29; N, 12.22

Example 129

Synthesis of N-[1-(N-methyl-N-phenylaminocarbonylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride
15

1) The procedure of Example 125-1) was generally followed to provide N-[1-(N-methyl-N-phenylaminocarbonylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red oil.

20 ¹H-NMR (200 MHz, CDCl₃) δ: 1.18-1.53 (3H, m), 1.55-1.68 (2H, m), 1.88-2.05 (2H, m), 2.78-2.95 (2H, m), 2.912 (2H, s), 3.150 (2H, t like, J=5.9 Hz), 3.266 (3H, s), 5.763 (1H, dd, J=2.8, 5.4 Hz), 6.433 (1H, br s), 6.60-6.63 (2H, m), 6.700 (1H, s), 6.991 (1H, s), 7.16-7.22 (2H, m), 7.29-7.48 (3H, m).

25 2) The procedure of Example 125-2) was generally followed to provide N-[1-(N-methyl-N-phenylaminocarbonylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride
30 as orange-colored crystals.

35 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.40-1.95 (4H, m), 2.82-3.10 (3H, m), 3.10-3.55 (4H, m), 3.243 (3H, s), 3.80-3.91 (2H, m), 6.651 (1H, d, J=7.6 Hz), 7.003 (1H, d, J=9.2 Hz), 7.25-7.60 (6H, m), 7.694 (1H, s), 9.00-9.15 (1H, m), 9.632 (1H, br s).
IR (KBr): 3400, 3230, 3050, 2950, 1650, 1630, 1590,

1560, 1535, 1500, 1455, 1435, 1360, 1290, 1210,
1130, 1110, 1040, 950, 780, 700, 620 cm⁻¹.

Example 130

5 **Synthesis of N-[1-(3,3-diphenylpropan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride**

10 1) The procedure of Example 38-1) was generally followed to provide N-[1-(3,3-diphenylpropan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as deep red foam.

15 ¹H-NMR (CDCl₃) δ: 1.30-1.75 (5H, m), 1.90-2.05 (2H, m), 2.20-2.60 (4H, m), 2.98 (2H, br d, 11.4 Hz), 3.19 (2H, t, J=5.9 Hz), 3.95 (1H, br t, 6.6 Hz), 5.78 (1H, dd, 1.8, 5.8 Hz), 5.95-6.05 (1H, m), 6.57-6.70 (2H, m), 6.72 (1H, s), 7.04 (1H, s), 7.10-7.35 (10H, m).

20 IR (KBr): 3359, 3059, 3026, 2927, 2810, 1618, 1543, 1510, 1481, 1452, 1282, 1155, 970, 771, 752, 735, 702 cm⁻¹.

25 2) **Synthesis of N-[1-(3,3-diphenylpropan-1-yl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride**

30 Using the above compound, the procedure of Example 1-6) was generally followed to provide the title compound as orange-colored solid.

35 ¹H-NMR (CD₃OD) δ: 1.40-1.70 (2H, m), 1.80-2.00 (3H, m), 2.50-2.65 (2H, m), 2.80-3.10 (4H, m), 3.19 (2H, d, 5.8 Hz), 3.50-3.65 (2H, m), 4.02 (1H, t, 7.7 Hz), 6.60 (1H, d, 7.6 Hz), 6.96-7.01 (2H, m), 7.15-7.45 (11H, m), 7.51 (1H, s).

40 IR (KBr): 3388, 3061, 2933, 2694, 1635, 1564, 1535, 1498, 1454, 1394, 1290, 1215, 1103, 781, 704 cm⁻¹.

45 Elemental analysis for C₃₁H₃₄N₄OSCl₂•1.5H₂O

Calcd.: C, 61.18; H, 6.13; N, 9.21

50 Found : C, 61.15; H, 6.21; N, 9.32

Example 131

Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[(1-ethoxycarbonyl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene carboxamide

To a solution of 2.02 g (9.26 mM) of 5-thia-1,8b-diazaacenaphthylene carboxylic acid in acetonitrile (30 ml) was added 2.13 g (18.51 mM) of N-hydroxysuccinimide and 3.55 g (18.52 mM) of N-ethyl-N'-3-(N,N-dimethylamino)propyl carbodiimide hydrochloride, and the mixture was stirred at room temperature for 2 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with chloroform. The extract was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄ and the solvent was distilled off under reduced pressure. To a solution of the residue in acetonitrile (27 ml) was added a mixture of 1.9 ml (11.08 mM) of ethyl 4-aminopiperidinecarboxylate and 2.5 ml (17.9 mM) of triethylamine in acetonitrile (5 ml), and the mixture was stirred at room temperature for 2 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with methylene chloride. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate 20%) to provide 3.12 g (91%) of N-[(1-ethoxycarbonyl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene carboxamide as red amorphous substance.

¹H-NMR (CDCl₃) δ: 1.16-1.46 (m, 2H), 1.26 (t, J=7.0 Hz, 3H), 1.93-2.02 (m, 2H), 2.84-2.97 (m, 2H), 3.87-4.21 (m, 2H), 4.13 (q, J=7.0 Hz, 2H), 5.67 (br d, J=8.0 Hz, 1H), 5.80 (dd, J=1.8, 6.2 Hz, 1H), 6.59-

6.71 (m, 3H), 7.05 (s, 1H).

2) Synthesis of N-(1-tert-butoxycarbonylpiperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene carboxamide

Under argon gas, 1.8 ml (12.65 mM) of trimethylsilyl iodide was added to a solution of 1.58 g (4.24 mM) of N-[(N-ethoxycarbonyl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene carboxamide in acetonitrile (35 ml) at room temperature and the mixture was stirred for 16 hours. Then, 1.2 ml (8.43 mM) of trimethylsilyl iodide was further added and the mixture was stirred at room temperature for 2 days. The reaction was stopped by adding methanol and the reaction mixture was stirred at room temperature for 2 hours. To this mixture were added 4 ml (28.7 mM) of triethylamine and 1.07 ml (4.66 mM) of di-tert-butyl dicarbonate at room temperature and the mixture was stirred for 10 minutes. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with methylene chloride. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate 10%) to provide 2.12 g of N-(1-tert-butoxycarbonylpiperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene carboxamide as red amorphous substance.

¹H-NMR (CDCl₃) δ: 1.13-1.99 (m, 2H), 1.46 (s, 9H), 1.73-1.98 (m, 2H), 2.74-2.95 (m, 2H), 3.84-4.18 (m, 3H), 5.70-5.85 (m, 1H), 5.79 (dd, J=1.9, 5.7 Hz, 1H), 6.58-6.72 (m, 3H), 7.04 (s, 2H).

3) Synthesis of N-(piperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene carboxamide dihydrochloride
To 2.12 g of N-(1-tert-butoxycarbonylpiperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene carboxamide was added 10 ml of concentrated hydrochloric acid and the

mixture was stirred at room temperature for 2 hours. The solid matter was filtered off and ethanol was added to the filtrate. After the solvent was distilled off under reduced pressure, ethanol was added again and the mixture was concentrated. The above procedure was repeated a few times and the resulting crystals were collected by filtration. This crystal crop was rinsed with ethanol and diethyl ether to provide 0.95 g (60%) of N-(piperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as orange-colored solid.

¹H-NMR (D₂O) δ: 1.64-1.87 (m, 2H), 2.03-2.19 (m, 2H), 3.03-3.21 (m, 2H), 3.42-3.58 (m, 2H), 3.82-4.02 (m, 1H), 5.98 (d, J=7.0 Hz, 1H), 6.60 (d, J=9.2 Hz, 1H), 6.67 (s, 1H), 6.78 (dd, J=7.2, 9.2 Hz, 1H), 6.98 (s, 1H).

4) Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 3.0 g (8.84 mM) of N-(piperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride and 4.1 ml (29.4 mM) of triethylamine in ethanol (40 ml) was added 1.6 ml (10.53 mM) of 3-phenyl-1-bromopropane at room temperature and the mixture was refluxed under nitrogen for 16 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate 20-40%) to provide 2.91 g (86%) of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red-purple amorphous substance.

¹H-NMR (CDCl₃) δ: 1.41-1.64 (m, 2H), 1.75-2.21 (m, 6H),

2.31-2.47 (m, 2H), 2.63 (t, J=7.7 Hz, 2H), 7.79-
2.96 (m, 2H), 3.72-3.92 (m, 1H), 5.75-5.80 (m,
2H), 6.57-6.69 (m, 1H), 7.03 (s, 1H), 7.16-7.32
(m, 5H).

5 5) Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-
y1]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
dihydrochloride

To a solution of 2.91 g (6.95 mM) of N-[1-(3-
phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-
10 diazaacenaphthylene-4-carboxamide in ethanol (10 ml)
was added 10 ml (40 mM) of 4N-HCl/methanol at room
temperature and the mixture was stirred at room
temperature for several minutes. After the solvent was
distilled off under reduced pressure, ethanol and
15 diethyl ether were added to the residue. The resulting
crystals were collected by filtration and rinsed with
ethanol and diethyl ether to provide 3.08 g (90%) of N-[
1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-
diazaacenaphthylene-4-carboxamide dihydrochloride as
20 orange-colored solid.

¹H-NMR (DMSO-d₆) δ: 1.80-2.14 (m, 6H), 2.63 (t, J=7.5
Hz, 2H), 2.82-3.11 (m, 4H), 3.38-3.56 (m, 2H),
3.72-3.93 (m, 1H), 6.64 (d, J=6.6 Hz, 1H), 6.99
(d, J=9.2 Hz, 1H), 7.15-7.38 (m, 7H), 7.67 (s,
25 1H), 8.80-8.90 (m, 1H).

Elemental analysis for C₂₄H₂₈N₄OSCl₂•2.5H₂O

Calcd.: C, 53.73; H, 6.20; N, 10.44

Found : C, 53.84; H, 6.06; N, 10.28

Example 132

30 Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-
5-thia-1,8b-diazaacenaphthylene-4-carboxamide

1) Synthesis of tert-butyl 4-aminopiperidine-1-
carboxylate 1/2 potassium hydrogen sulfate salt

To a solution of 50 g (262.8 mM) of 4-amino-1-
35 benzylpiperidine in 500 ml of methanol was added 5 g of
5% palladium-on-carbon (hydrous) and catalytic

reduction was carried out at the hydrogen pressure of 5 kg/cm² at 35°C for 15 hours. The catalyst Pd/carbon was then filtered off and the filtrate was concentrated under reduced pressure to provide 4-aminopiperidine.

5 To a solution of this 4-aminopiperidine in toluene (500 ml) was added 27.89 g (262.8 mM) of benzaldehyde and the mixture was refluxed for 3 hours, with the byproduct water being removed with a Dean-Stark trap. After cooling to room temperature, 63.08 g (289 mM) of
10 di-tert-butyl dicarbonate was added dropwise gradually over about 1 hour and the mixture was stirred at room temperature overnight. After the solvent was distilled off under reduced pressure, 290 ml of 1N-aqueous solution of potassium hydrogen sulfate was added to the
15 residue at room temperature and the mixture was stirred for 2 hours. The resulting crystal crop was harvested by filtration and rinsed with water, ethanol, and diethyl ether to provide tert-butyl 4-aminopiperidine-1-carboxylate 1/2 potassium hydrogen sulfate salt as
20 colorless crystals (49.02 g, 71%).

¹H-NMR (200 MHz, CD₃CO₂D) δ: 1.47 (s, 9H), 1.52-1.73 (m, 2H), 2.01-2.18 (m, 2H), 2.75-2.98 (m, 2H), 3.41-3.59 (m, 1H), 4.10-4.32 (m, 2H).

IR (KBr): 1689, 1621, 1543, 1429, 1369, 1252, 1151,
25 1065, 862, 766, 617 cm⁻¹.

2) Synthesis of N-(1-tert-butoxycarbonylpiperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene carboxamide dihydrochloride

To a suspension of 12.88 g (53.8 mM) of 5-thia-1,8b-diazaacenaphthylene carboxylic acid in acetonitrile (27 ml) were added 12.38 g (107.6 mM) of N-hydroxysuccinimide and 20.63 g (107.6 mM) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride, and the mixture was stirred at room temperature for 2 hours. To this reaction mixture was added a solution of 17.3 g (64.5 mM) of tert-butyl 4-

aminopiperidine-1-carboxylate 1/2 potassium hydrogen sulfate salt, 19.6 g (128.7 mM) of 1,8-diazabicyclo[5.4.0]-7-undecene, and 7.5 ml (53.8 mM) of triethylamine in acetonitrile (80 ml) and the mixture was stirred for 64 hours. After the solvent was distilled off under reduced pressure, small amounts of ethanol and ethyl acetate were added to the residue. The organic layer was washed serially with water and saturated aqueous solution of sodium chloride and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate 10%) to provide 22.48 g of N-(1-tert-butoxycarbonylpiperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene carboxamide as red amorphous substance.

15 ¹H-NMR (CDCl₃) δ: 1.16-1.46 (m, 2H), 1.26 (t, J=7.0 Hz, 3H), 1.93-2.02 (m, 2H), 2.84-2.97 (m, 2H), 3.87-4.21 (m, 2H), 4.13 (q, J=7.0 Hz, 2H), 5.67 (br d, J=8.0 Hz, 1H), 5.80 (dd, J=1.8, 6.2 Hz, 1H), 6.59-6.71 (m, 3H), 7.05 (s, 1H).

20 3) Synthesis of N-(piperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene carboxamide dihydrochloride
To 22.48 g of N-(1-tert-butoxycarbonylpiperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene carboxamide was added 40 ml of concentrated hydrochloric acid and the mixture was stirred at room temperature for 2 hours. To this reaction mixture was added ethanol and the resulting crystals were collected by filtration. This crystal crop was rinsed with ethanol and diethyl ether to provide 14.68 g (73%) of N-(piperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene carboxamide dihydrochloride as orange-colored crystals.

25 ¹H-NMR (D₂O) δ: 1.64-1.87 (m, 2H), 2.03-2.19 (m, 2H), 3.03-3.21 (m, 2H), 3.42-3.58 (m, 2H), 3.82-4.02 (m, 1H), 5.98 (d, J=7.0 Hz, 1H), 6.60 (d, J=9.2 Hz, 1H), 6.67 (s, 1H), 6.78 (dd, J=7.2, 9.2 Hz,

1H), 6.98 (s, 1H).

4) Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a solution of 12.0 g (32.1 mM) of N-(piperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene carboxamide dihydrochloride and 22.4 ml (160.7 mM) of triethylamine was added 5.9 ml (38.8 mM) of 3-phenyl-1-bromopropane at room temperature and the mixture was refluxed under nitrogen for 20 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄ and the solvent was distilled off under reduced pressure.

The residue was purified by silica gel column chromatography (methanol/ethyl acetate 20-40%). The crystals obtained were dissolved in ethanol (100 ml)-chloroform (100 ml) and the chloroform was distilled off by heating under atmospheric pressure. After concentration to about 80 ml, the residue was allowed to stand at room temperature and the resulting crystals were collected by filtration to provide 7.04 g (52%) of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as red crystals.

m.p. 187-188°C

¹H-NMR (CDCl₃) δ: 1.41-1.64 (m, 2H), 1.75-2.21 (m, 6H), 2.31-2.47 (m, 2H), 2.63 (t, J=7.7 Hz, 2H), 7.79-2.96 (m, 2H), 3.72-3.92 (m, 1H), 5.75-5.80 (m, 2H), 6.57-6.69 (m, 1H), 7.03 (s, 1H), 7.16-7.32 (m, 5H).

Elemental analysis for C₂₄H₂₆N₄OS

Calcd.: C, 68.87; H, 6.26; N, 13.39

Found : C, 68.62; H, 6.25; N, 13.42

Example 133

35 Synthesis of N-[1-[2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethyl]piperidin-4-ylmethyl]-5-thia-1,8b-

diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[1-[2-(6-tert-butyldimethylsiloxy-
2,5,7,8-tetramethylchroman-2-yl)ethyl]piperidin-4-yl-
methyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

5 Under nitrogen gas, 0.46 ml (5.94 mM) of methane-sulfonyl chloride was added to a solution of 1.46 g (4.00 mM) of 6-tert-butyldimethylsiloxy-2-(2-hydroxyethyl)-2,5,7,8-tetramethylchroman and 1.11 ml (7.96 mM) of triethylamine in diethyl ether (8 ml) at
10 0°C and the mixture was stirred at the prevailing temperature for 30 minutes. The reaction was stopped by adding saturated aqueous solution of sodium hydrogen carbonate and the reaction mixture was extracted with diethyl ether. The organic layer was washed serially
15 with water and saturated aqueous solution of sodium chloride and dried over MgSO₄. The solvent was then distilled off under reduced pressure to provide the crude mesylate (1.76 g) as light-yellow oil. This crude mesylate (1.76 g, 3.98 mM) was added to a
20 solution of 0.77 g (1.99 mM) of N-(piperidin-4-ylmethyl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride and 1.4 ml (10.0 mM) of triethylamine in ethanol (7 ml) and the mixture was refluxed under nitrogen for 18 hours. This reaction mixture was
25 diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. After concentration, the crude product was purified by column chromatography (methanol/ethyl acetate 20-40%)
30 to provide the title compound as red amorphous substance.

Yield 1.00 g (76%)

¹H-NMR (CDCl₃) δ: 0.11 (s, 6H), 1.04 (s, 9H), 1.24 (s, 3H), 1.42-2.01 (m, 11H), 2.04 (s, 3H), 2.06 (s, 3H), 2.09 (s, 3H), 2.45-2.61 (m, 4H), 2.84-3.00 (m, 2H), 3.17-3.23 (m, 2H), 5.72-5.84 (m, 1H),

5.80 (dd, $J=1.6$, 6.2 Hz, 1H), 6.59-6.74 (m, 3H),
7.06 (s, 1H).

IR (KBr): 3442, 2929, 1622, 1545, 1468, 1257, 1153,
1092, 837, 773 cm^{-1} .

5 2) Synthesis of N-[1-[2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethyl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 1.00 g (1.51 mM) of N-[1-[2-(6-tert-butyldimethylsiloxy-2,5,7,8-tetramethylchroman-2-yl)ethyl]piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (4 ml) was added 4.0 ml (16 mM) of 4N-HCl/methanol and the mixture was stirred at room temperature for 63 hours. After the solvent was distilled off under reduced pressure, ethanol was added and the mixture was stirred at room temperature for 1 hour. The resulting crystal crop was harvested by filtration and rinsed with ethanol and diethyl ether to provide the title compound as orange-colored crystals.

20 Yield 789.4 mg (84%)

$^1\text{H-NMR}$ (DMSO- d_6) δ: 1.19 (s, 3H), 1.36-2.08 (m, 11H),
1.99 (s, 3H), 2.02 (s, 3H), 2.05 (s, 3H), 2.76-
3.55 (m, 8H), 6.58 (d, $J=7.0$ Hz, 1H), 6.96 (d,
 $J=8.4$ Hz, 1H), 7.17-7.30 (m, 2H), 7.63 (s, 1H),
8.84-8.96 (m, 1H), 10.07-10.32 (m, 1H).

25 IR (KBr): 3392, 1635, 1564, 1450, 1294, 1253, 1161,
1088, 995, 789 cm^{-1} .

Elemental analysis for $C_{31}H_{40}N_4O_3SCl_2 \cdot 2.0H_2O$

Calcd.: C, 56.79; H, 6.76; N, 8.54

30 Found : C, 56.93; H, 6.79; N, 8.35

Example 134

Synthesis of N-[1-[2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethyl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

35 1) Synthesis of N-[1-[2-(6-tert-butyldimethylsiloxy-2,5,7,8-tetramethylchroman-2-yl)ethyl]piperidin-4-yl]-

5-thia-1,8b-diazaacenaphthylene-4-carboxamide

Under nitrogen gas, 0.46 ml (5.94 mM) of methane-sulfonyl chloride was added to a solution of 1.46 g (4.00 mM) of 6-tert-butyldimethylsiloxy-2-(2-hydroxyethyl)-2,5,7,8-tetramethylchroman and 1.11 ml (7.96 mM) of triethylamine in diethyl ether (8 ml) at 0°C and the mixture was stirred at the prevailing temperature for 30 minutes. The reaction was stopped by adding saturated aqueous solution of sodium hydrogen carbonate and the reaction mixture was extracted with diethyl ether. The organic layer was washed serially with water and saturated aqueous solution of sodium chloride and dried over MgSO₄. The solvent was then distilled off under reduced pressure to provide crude mesylate (1.75 g) as light-yellow oil. To a solution of 0.93 g (2.4 mM) of N-(piperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride and 1.7 ml (12.2 mM) of triethylamine in ethanol (10 ml) was added the above mesylate (1.75 g) at room temperature and the mixture was refluxed under nitrogen for 16 hours. This reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. After concentration, the crude product obtained was purified by column chromatography (methanol/-ethyl acetate 20-30%) to provide the title compound as red amorphous substance.

¹H-NMR (200 MHz, CDCl₃) δ: 0.11 (s, 6H), 1.04 (s, 9H), 1.25 (s, 3H), 1.68-2.22 (m, 8H), 2.05 (s, 6H), 2.09 (s, 3H), 2.24-2.90 (m, 6H), 3.03-3.22 (m, 2H), 3.79-4.02 (m, 2H), 5.79 (dd, J=1.8, 5.8 Hz), 5.97-6.09 (m, 1H), 6.57-6.69 (m, 2H), 6.73 (s, 1H), 7.06 (s, 1H).
IR (KBr): 3444, 2943, 1624, 1251, 1153, 1092, 837, 773 cm⁻¹.

2) Synthesis of N-[1-[2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethyl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 1.17 g (1.78 mM) of N-[1-[2-(6-tert-butyldimethylsiloxy-2,5,7,8-tetramethylchroman-2-yl)ethyl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (5 ml) was added 5.0 ml (20 mM) of 4N-HCl/methanol and the mixture was stirred at room temperature for 90 hours. After the solvent was distilled off under reduced pressure, ethanol and diethyl ether were added and the resulting crystals were collected by filtration and rinsed with ethanol and diethyl ether to provide the title compound as orange-colored crystals.

15 Yield 867.3 mg (80%)

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.19 (s, 3H), 1.62-2.13 (m, 8H), 2.00 (s, 3H), 2.02 (s, 3H), 2.06 (s, 3H), 2.43-2.65 (m, 2H), 2.80-3.59 (m, 6H), 3.71-4.08 (m, 1H), 6.62 (d, J=7.8 Hz, 1H), 6.98 (d, J=8.8 Hz, 1H), 7.22 (s, 1H), 7.29 (dd, J=7.6, 8.8 Hz, 2H), 7.65 (s, 1H), 8.72-8.91 (m, 1H), 10.37-10.79 (m, 1H).

IR (KBr): 3396, 1635, 1533, 1450, 1306, 1257, 1219 cm⁻¹.

25 Example 135

Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl-methyl]-3,4-dihydro-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of ethyl 3,4-dihydro-5-thia-1,8b-diazaacenaphthylene-4-carboxylate

To a solution of 11.8 g (50 mM) of ethyl imidazo[1,2-a]pyridine-5-thiaacetate in acetonitrile (250 ml) was added 13.9 g (75 mM) of N,N-dimethylmethylenammonium iodide and the mixture was refluxed for 2 hours. After cooling to room temperature, the solvent was distilled off under

reduced pressure and the residue was dissolved in dichloromethane. This solution was washed with saturated aqueous solution of sodium hydrogen carbonate and saturated aqueous solution of sodium chloride,
5 dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate 10-20%) to provide the title compound as red-purple oil.

Yield 5.13 g (41%)

10 ¹H-NMR (200 MHz, CDCl₃) δ: 1.19 (t, 3H, J=7.2 Hz),
3.63-3.80 (m, 2H), 4.05-4.22 (m, 3H), 6.78 (d,
J=7.0 Hz, 1H), 7.09-7.17 (m, 1H), 7.48 (d, J=8.4
Hz, 1H), 7.53 (s, 1H).

2) Synthesis of N-[(1-tert-butoxycarbonyl-4-piperidyl)-
15 methyl]-3,4-dihydro-5-thia-1,8b-diazaacenaphthylene-4-
carboxamide

To a solution of 5.13 g (20.7 mM) of ethyl 3,4-dihydro-5-thia-1,8b-diazaacenaphthylene-4-carboxylate in ethanol (20 ml) was added 12 ml (24 mM) of 2N-aqueous solution of sodium hydroxide at room temperature and the mixture was stirred for 1 hour. To this reaction mixture was added 4 ml (24 mM) of 6N-hydrochloric acid and the resulting crystals were collected by filtration. This crystal crop was rinsed with ethanol and diethyl ether to provide 3,4-dihydro-5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid as light-brown crystals. This carboxylic acid was not purified but used as it was in the next reaction. To 2.2 ml (30.0 mM) of thionyl chloride was added 661 mg (3.0 mM) of the above 3,4-dihydro-5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and the mixture was heated at 60°C for 1 hour. Then, the excess thionyl chloride was distilled off under reduced pressure and 10 ml of toluene was added to the residue.
30 After thorough mixing, the solvent was distilled off under reduced pressure to provide 3,4-dihydro-5-thia-

1,8b-diazaacenaphthylene-4-carboxylic acid chloride hydrochloride. To a solution of this acid chloride in 30 ml of THF was added 2.5 ml (40.0 mM) of triethylamine as well as 1286 mg (6.0 mM) of 1-(tert-butoxycarbonyl)-4-aminomethylpiperidine at 0°C and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was then poured in 50 ml of iced water and extracted with 100 ml of ethyl acetate. The organic layer was washed with 100 ml of saturated aqueous solution of sodium chloride and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/ethanol = 10/1) to provide 801 mg (yield 64.1%) of the title compound as brown amorphous substance.

¹H-NMR (200 MHz, CDCl₃) δ: 0.72-1.01 (m, 2H), 1.25-1.38 (m, 3H), 2.38-2.61 (m, 2H), 2.83-3.02 (m, 1H), 3.08-3.27 (m, 1H), 3.62 (dd, 1H, J=17.4 Hz, 7.0 Hz), 3.87-4.09 (m, 4H), 6.66 (t, 1H, NH, J=5.8 Hz), 6.77 (d, 1H, J=7.2 Hz), 7.11 (dd, 1H, J=9.2, 7.2 Hz), 7.45 (d, 1H, J=9.2 Hz), 7.51 (s, 1H). IR (KBr): 1666, 1385, 1188 cm⁻¹.

3) Synthesis of N-(4-piperidyl)methyl-3,4-dihydro-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 480 g (1.15 mM) of N-[(1-tert-butoxycarbonyl-4-piperidyl)methyl]-3,4-dihydro-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in 20 ml of 2-propanol was added 0.47 ml (5.76 mM) of 12N-hydrochloric acid and the mixture was stirred at room temperature for 1 hours. This reaction mixture was concentrated under reduced pressure and the resulting crystals were collected by filtration and rinsed with a small amount of ether to provide 404 mg (90.2%) of the title compound as white crystals.

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.18-1.53 (m, 2H), 1.58-

1.85 (m, 3H), 2.64-2.88 (m, 2H), 3.12-3.36 (m, 4H), 3.63-3.75 (m, 2H), 4.65 (t, 1H, J=5.8 Hz), 7.51 (dd, 1H, J=6.4, 2.2 Hz), 7.77-7.92 (m, 2H), 8.18 (s, 1H), 9.04 (t, 1H, NH, J=5.4 Hz), 9.20 (br s, 2H, NH).

5 IR (KBr): 1649, 1554, 1504 cm⁻¹.

4) Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-ylmethyl]-3,4-dihydro-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

10 To a solution of 746.4 mg (1.91 mM) of N-(4-piperidyl)methyl-3,4-dihydro-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride and 1.4 ml (10.0 mM) of triethylamine in ethanol (5 ml) was added 0.35 ml (2.30 mM) of 1-bromo-3-phenylpropane at room temperature and the mixture was refluxed under nitrogen for 64 hours. This reaction mixture was diluted with water and extracted with chloroform, and the organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. The residue was purified by column chromatography (methanol/ethyl acetate 20-30-50%) to provide the title compound as red amorphous substance.

20 Yield 583.9 mg (70%)

25 ¹H-NMR (200 MHz, CDCl₃) δ: 1.06-1.38 (m, 4H), 1.70-1.92 (m, 3H), 1.96-2.25 (m, 2H), 2.33-2.41 (m, 2H), 2.56-2.64 (m, 2H), 2.79-3.00 (m, 3H), 3.08-3.26 (m, 1H), 3.57-3.72 (m, 1H), 3.97-4.10 (m, 2H), 6.53-6.69 (m, 1H), 6.78 (dd, J=7.0, 1.0 Hz, 1H), 7.03-7.34 (m, 6H), 7.45 (dd, J=9.2, 1.0 Hz, 1H), 7.53 (s, 1H).

30 IR (KBr): 3304, 2926, 1657, 1620, 1556, 1481, 1306, 1140 cm⁻¹.

35 5) Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-ylmethyl]-3,4-dihydro-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 583.9 mg (1.34 mM) of N-[1-(3-

phenylpropan-1-yl)piperidin-4-ylmethyl]-3,4-dihydro-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (5 ml) was added 10 ml (40 mM) of 4N-HCl/methanol and the mixture was stirred at room temperature for several minutes. After the solvent was distilled off under reduced pressure, 2-propanol was added and the resulting crystals were filtered off. The filtrate was concentrated to provide the title compound as light-brown amorphous substance.

Yield 542.5 mg (80%)

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.35-1.86 (m, 3H), 1.94-2.20 (m, 2H), 2.44-3.23 (m, 10H), 3.32-4.00 (m, 4H), 4.51-4.68 (m, 1H), 7.10-7.41 (m, 5H), 7.43-7.59 (m, 1H), 7.72-7.92 (m, 2H), 8.16 (s, 1H), 8.87-9.08 (m, 1H), 10.53-10.82 (m, 1H).
IR (KBr): 3421, 3064, 2933, 2721, 1662, 1551, 1502, 1441, 1365, 1215 cm⁻¹.

Example 136

Synthesis of N-[trans-4-(4-phenylpiperidin-1-ylmethyl)-1-cyclohexylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[trans-4-(4-phenylpiperidin-1-ylmethyl)-1-cyclohexylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a solution of 0.41 g (1.88 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 0.37 g (3.21 mM) of N-hydroxysuccinimide in acetonitrile (5 ml) was added 0.62 g (3.23 mM) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide at room temperature, and the mixture was stirred for 1 hour. To this reaction mixture was added a suspension of 0.70 g (1.95 mM) of 1-(trans-4-aminomethyl-1-cyclohexylmethyl)-4-phenylpiperidine dihydrochloride and 1.0 ml (7.71 mM) of triethylamine in chloroform (10 ml) and the mixture was further stirred for 2 hours. The solvent was then distilled off under reduced pressure and the residue

was diluted with water and a small amount of ethanol and extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride and dried over $MgSO_4$. After concentration,

5 the crude product obtained was purified by column chromatography (methanol/ethyl acetate 30-50%) and recrystallization from ethyl acetate to provide the title compound as red-purple crystals.

Yield 576.9 mg (63%)

10 1H -NMR (200 MHz, $CDCl_3$) δ : 0.78-1.03 (m, 4H), 1.62-2.03 (m, 12H), 2.20 (d, $J=7.0$ Hz, 2H), 2.39-2.59 (m, 1H), 2.94-3.08 (m, 2H), 3.11-3.23 (m, 2H), 5.72-5.84 (m, 1H), 5.79 (dd, $J=6.2, 1.6$ Hz, 1H), 6.58-6.74 (m, 3H), 7.06 (s, 1H), 7.12-7.36 (m, 5H).

15 IR (KBr): 3336, 2922, 1618, 1533, 1277, 1161 cm^{-1} .

2) Synthesis of N-[trans-4-(4-phenylpiperidin-1-ylmethyl)-1-cyclohexylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 549.7 mg (1.13 mM) of N-[trans-4-(4-phenylpiperidin-1-ylmethyl)-1-cyclohexylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (5 ml) was added 1.0 ml (12.0 mM) of 12N-hydrochloric acid and the mixture was stirred at room temperature for several minutes. After the reaction mixture was concentrated under reduced pressure, diethyl ether was added to the residue and the resulting crystals were collected by filtration and rinsed with ethanol and diethyl ether to provide the title compound as orange-colored crystals.

25 Yield 541.1 mg (86%)

30 1H -NMR (200 MHz, $DMSO-d_6$) δ : 0.80-1.12 (m, 4H), 1.29-2.09 (m, 8H), 2.14-2.41 (m, 2H), 2.65-3.17 (m, 7H), 3.44-3.62 (m, 2H), 6.63 (d, $J=6.8$ Hz, 1H), 6.99 (d, $J=8.2$ Hz, 1H), 7.19 (s, 1H), 7.21-7.42 (m, 6H), 7.67 (s, 1H), 8.81 (t, $J=5.6$ Hz, 1H), 10.14-10.40 (m, 1H).

IR (KBr): 3417, 2924, 1635, 1564, 1535, 1500, 1441,
1292 cm⁻¹.

Elemental analysis for C₂₉H₃₆N₄O₂SCl₂•1.5H₂O

Calcd.: C, 59.38; H, 6.70; N, 9.55

5 Found : C, 59.10; H, 6.65; N, 9.55

Example 137

Synthesis of N-[1-(4-phenylbutan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

10 1) Synthesis of N-[1-(4-phenylbutan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a solution of 72.5 mg (1.94 mM) of N-(piperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride and 1.4 ml (10.0 mM) of triethylamine in ethanol (7 ml) was added 0.61 g (2.33 mM) of 1-iodo-4-phenylbutane at room temperature and the mixture was refluxed under nitrogen for 6 hours. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over MgSO₄, and concentrated. The resulting crude product was purified by column chromatography (methanol/ethyl acetate 30%) and recrystallization from ethyl acetate to provide the title compound as light-purple crystals.

20 Yield 495.2 mg (59%)
m.p. 183-185°C

30 ¹H-NMR (200 MHz, CDCl₃) δ: 1.47-1.68 (6H, m), 1.86-2.03 (2H, m), 2.12-2.29 (2H, m), 2.39-2.51 (2H, m), 2.57-2.72 (2H, m), 2.89-3.05 (2H, m), 3.74-3.97 (1H, m), 5.78 (1H, dd, J=6.2, 1.8 Hz), 5.81-5.92 (1H, m), 6.58-6.70 (3H, m), 7.05 (1H, s), 7.11-7.35 (5H, m).

35 IR (KBr): 3298, 2941, 1612, 1535, 1277, 1159 cm⁻¹.

35 2) Synthesis of N-[1-(4-phenylbutan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

dihydrochloride

To a solution of 437.4 mg (1.01 mM) of N-[1-(4-phenylbutan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (10 ml) was added 5 0.5 ml (6 mM) of 12N-hydrochloric acid and the mixture was stirred at room temperature for 16 hours. After this reaction mixture was concentrated, a small amount of ethanol was added to the residue and the crystals were collected by filtration and rinsed with ethanol 10 and diethyl ether to provide the title compound as orange-colored crystals.

Yield 431.1 mg (84%)

m.p. 232-237°C (dec.)

15 $^1\text{H-NMR}$ (200 MHz, DMSO- d_6) δ : 1.48-2.02 (8H, m), 2.54-2.67 (2H, m), 2.77-3.15 (4H, m), 3.24-3.53 (2H, m), 3.70-4.08 (1H, m), 6.54 (1H, d, $J=7.4$ Hz), 6.93 (1H, d, $J=9.2$ Hz), 7.10-7.36 (7H, m), 7.58 (1H, s), 8.64-8.71 (0.2H, m), 8.78 (0.8H, d, $J=7.2$ Hz), 10.06-10.25 (0.2H, m), 10.38-10.60 (0.8H, m).
20 IR (KBr): 3415, 2939, 1632, 1566, 1535, 1500, 1304, 1213 cm^{-1} .

Elemental analysis for $\text{C}_{25}\text{H}_{30}\text{N}_4\text{OSCl}_2 \cdot 2.0\text{H}_2\text{O}$

Calcd.: C, 55.45; H, 6.33; N, 10.35

Found : C, 55.46; H, 6.21; N, 10.56

25 Example 138

Synthesis of N-[1-[3-(4-fluorophenyl)propan-1-yl]-piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

30 1) Synthesis of N-[1-[3-(4-fluorophenyl)propan-1-yl]-piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

Under nitrogen gas, 0.47 ml (6.07 mM) of methane-sulfonyl chloride was added to a solution of 0.62 g (4.02 mM) of 3-(4-fluorophenyl)propanol and 1.1 ml (7.89 mM) of triethylamine in diethyl ether (8 ml) at 35 0°C and the mixture was stirred at the prevailing

temperature for 1 hour. The reaction was stopped by adding saturated aqueous solution of sodium hydrogen carbonate and the reaction mixture was extracted with diethyl ether. The organic layer was washed with 5 saturated aqueous solution of sodium chloride and dried over MgSO₄. The solvent was then distilled off under reduced pressure to recover the crude mesylate. This crude product was not purified but used as it was in the next reaction. To a solution of 0.75 g (2.00 mM) 10 of N-(piperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride and 1.4 ml (10.0 mM) of triethylamine in ethanol (8 ml) was added 0.94 g (<4.02 mM) of the above crude mesylate at room temperature and the mixture was refluxed under nitrogen for 16 hours. 15 After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over MgSO₄, and concentrated. The crude product thus obtained was purified by column 20 chromatography (methanol/ethyl acetate 20-30-40%) and recrystallization from ethyl acetate-ethanol to provide the title compound as red-purple crystals.

Yield 405.2 mg (46%)

m.p. 117-119°C

25 ¹H-NMR (200 MHz, CDCl₃) δ: 1.35-1.65 (2H, m), 1.70-2.21 (6H, m), 2.31-2.42 (2H, m), 2.60 (2H, t, J=7.6 Hz), 2.72-2.96 (2H, m), 3.71-3.92 (1H, m), 5.66 (1H, br d, J=8.8 Hz), 5.78 (1H, dd, J=5.8, 1.6 Hz), 6.58-6.71 (3H, m), 6.91-7.16 (5H, m).
30 IR(KBr): 3284, 2941, 1614, 1535, 1508, 1281, 1160 cm⁻¹.
2) Synthesis of N-[1-[3-(4-fluorophenyl)propan-1-yl]-piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride
To a solution of 378.4 mg (0.86 mM) of N-[1-[(4-fluorophenyl)butan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in 5 ml of ethanol

was added 0.5 ml (6.0 mM) of 12N-hydrochloric acid at room temperature and the mixture was stirred for several minutes. After the solvent was distilled off under reduced pressure, 2-propanol and ethanol were 5 added to the residue. After concentration, diethyl ether was added and the resulting crystals were collected by filtration and rinsed with 2-propanol and diethyl ether to provide the objective compound as orange-colored crystals. This crystal crop was 10 dissolved in ethanol and, after concentration, diethyl ether was added. The resulting crystals were collected by filtration and rinsed with ethanol and diethyl ether to provide the title compound as orange-colored crystals.

15 Yield 433.5 mg (65%)

m.p. 164-174°C (dec.)

16 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.75-2.13 (6H, m), 2.54-2.70 (2H, m), 2.82-3.10 (4H, m), 3.23-3.57 (2H, m), 3.71-4.06 (1H, m), 6.58 (1H, d, J=7.0 Hz), 6.96 (1H, d, J=9.2 Hz), 7.05-7.36 (6H, m), 7.62 (1H, s), 8.68-8.78 (0.14H, m), 8.81 (0.86H, d, J=7.8 Hz), 10.45-10.62 (0.14H, m), 10.68-10.94 (0.86H, m).

IR (KBr): 3412, 1633, 1506, 1217 cm⁻¹.

20 Elemental analysis for C₂₄H₂₇N₄OSCl₂F•1.0H₂O

Calcd.: C, 54.65; H, 5.54; N, 10.62

Found : C, 54.29; H, 5.83; N, 10.37

Example 139

Synthesis of N-[4-(4-phenylpiperidin-1-ylmethyl)benzyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

30 1) Synthesis of N-[4-(4-phenylpiperidin-1-ylmethyl)-benzyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
To a suspension of 1.0 g (4.58 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 0.90 g (7.82 mM) of N-hydroxysuccinimide in acetonitrile (10 ml) was

added 1.51 g (7.88 mM) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride at room temperature, and the mixture was stirred for 1 hour. To this reaction mixture was added a solution of 1.67 g (4.73 mM) of 1-[4-(aminomethyl)benzyl]-4-phenylpiperidine dihydrochloride, 1.44 g (9.46 mM) of DBU, and 0.55 ml (3.95 mM) of triethylamine in acetonitrile (20 ml), and the mixture was further stirred for 4 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with ethyl acetate (a small amount of ethanol was additionally used). The organic layer was washed with saturated aqueous solution of sodium chloride and dried over MgSO₄. This crude product was purified by column chromatography (methanol/ethyl acetate 20-30%) to provide the title compound as red amorphous substance.

Yield 1.59 g (72%)

¹H-NMR (200 MHz, CDCl₃) δ: 1.68-1.89 (4H, m), 2.03-2.21 (2H, m), 2.39-2.60 (1H, m), 2.93-3.10 (2H, m), 3.56 (2H, s), 4.47 (2H, d, J=6.0 Hz), 5.77 (1H, dd, J=6.2, 1.8 Hz), 5.95-6.08 (1H, m), 6.62-6.70 (3H, m), 7.03 (1H, s), 7.17-7.21 (9H, m).

IR (KBr): 3295, 1615, 1543, 1481, 1281, 1155 cm⁻¹.
2) Synthesis of N-[4-(4-phenylpiperidin-1-ylmethyl)-benzyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 1.59 g (3.31 mM) of N-[4-(4-phenylpiperidin-1-ylmethyl)benzyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol was added 1 ml (12 mM) of 12N-hydrochloric acid at room temperature, and the mixture was stirred for several minutes. This reaction mixture was concentrated and, after addition of ethanol and diethyl ether, the crystal crop was harvested by filtration and rinsed with ethanol and diethyl ether to provide the title

compound as orange-colored crystals.

Yield 1.26 g (69%)

m.p. 269-275°C (dec.)

¹H-NMR (200 MHz, DMSO-d₆) δ: 1.83-2.00 (2H, m), 2.02-
5 2.29 (2H, m), 2.69-2.87 (1H, m), 2.90-3.14 (2H,
m), 3.30-3.46 (2H, m), 4.29 (2H, d, J=4.8 Hz),
4.37 (2H, d, J=6.0 Hz), 6.59 (1H, d, J=7.4 Hz),
6.96 (1H, d, J=8.8 Hz), 7.13-7.22 (9H, m), 7.55-
7.69 (3H, m), 9.35-9.47 (1H, m), 11.00-11.22 (1H,
10 m).

IR (KBr): 3391, 1642, 15001, 1298, 770 cm⁻¹.

Elemental analysis for C₂₉H₃₀N₄OSCl₂•1.0H₂O

Calcd.: C, 60.94; H, 5.64; N, 9.80

Found : C, 60.84; H, 5.73; N, 9.71

15 Example 140

Synthesis of N-[4-(4-benzylpiperidin-1-ylmethyl)benzyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[4-(4-benzylpiperidin-1-ylmethyl)-
20 benzyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a suspension of 1.0 g (4.58 mM) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid hydrochloride and 0.90 g (7.82 mM) of N-hydroxysuccinimide in acetonitrile (10 ml) was added 1.51 g (7.88 mM) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride at room temperature, and the mixture was stirred for 2 hours. To this reaction mixture was added a solution of 1.88 g (5.12 mM) of 1-[4-(aminomethyl)benzyl]-4-benzylpiperidine dihydrochloride and 0.55 ml (3.95 mM) of triethylamine in acetonitrile (20 ml) and the mixture was further stirred for 4 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water and extracted with ethyl acetate (a small amount of ethanol was additionally used). The organic layer was washed with saturated aqueous solution of sodium

chloride and dried over MgSO₄. The resulting crude product was purified by column chromatography (methanol/ethyl acetate 20%) to provide the title compound as red amorphous substance.

5 Yield 1.73 g (77%)

¹H-NMR (200 MHz, CDCl₃) δ: 1.20-2.03 (7H, m), 2.53 (2H, d, J=6.4 Hz), 2.79-2.93 (2H, m), 3.49 (2H, s), 4.46 (2H, d, J=5.4 Hz), 5.77 (1H, dd, J=6.2, 1.8 Hz), 5.93-6.08 (1H, m), 6.56-6.71 (3H, m), 7.03 (1H, s), 7.07-7.37 (9H, m).

10 IR (KBr): 3204, 1643, 1615, 1537, 1481, 1281, 1155, 772, 700 cm⁻¹.

2) Synthesis of N-[4-(4-benzylpiperidin-1-ylmethyl)-benzyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

15 To a solution of 1.73 g (3.50 mM) of N-[4-(4-benzylpiperidin-1-ylmethyl)benzyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (12 ml) was added 1 ml (12 mM) of 12N-hydrochloric acid at room temperature, and the mixture was stirred for several minutes (crystals separated out). This reaction mixture was concentrated under reduced pressure and ethanol and diethyl ether were added to the residue. The crystal crop was then harvested by filtration and rinsed with ethanol and diethyl ether to provide the title compound as orange-colored crystals.

20 Yield 1.48 g (75%)

m.p. 164-172°C

25 ¹H-NMR (200 MHz, DMSO-d₆) δ: 1.42-1.87 (5H, m), 2.68-2.95 (3H, m), 3.02-3.17 (1H, m), 3.18-3.33 (2H, m), 4.12-4.25 (2H, m), 4.35 (2H, d, J=4.6 Hz), 6.57 (1H, d, J=7.4 Hz), 6.96 (1H, d, J=9.2 Hz), 7.11-7.39 (9H, m), 7.50-7.65 (3H, m), 9.31-9.43 (1H, m), 10.49-10.79 (1H, m).

30 IR (KBr): 3217, 1634, 1566, 1537, 1505, 1298, 1217, 774, 700 cm⁻¹

Elemental analysis for C₃₀H₃₂N₄OSCl₂•0.5C₂H₅OH•1.5•H₂O

Calcd.: C, 60.28; H, 6.20; N, 9.07

Found : C, 60.27; H, 5.89; N, 9.08

Example 141

5 Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

1) Synthesis of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid

To a solution of 120.02 g (0.7991 mol) of imidazo-[1,2-a]pyridine-5-thiol and 134 ml (0.959 mol) of triethylamine in 500 ml of ethanol was added 88.6 ml (0.799 mol) of ethyl bromoacetate dropwise at room temperature, and the mixture was stirred at the same temperature for 2 hours. The solvent was then distilled off under reduced pressure and ethyl acetate was added to the residue. The resulting precipitate (for the most part, triethylamine hydrochloride) was filtered off and washed with ethyl acetate. The filtrate and washes were pooled and the solvent was distilled off under reduced pressure to provide ethyl (imidazo[1,2-a]pyridin-5-ylthio)acetate as crude product. This crude product was not purified but used as it was in the next reaction.

Brown liquid. Yield 199.7 g

25 To a solution of 199.7 g of crude ethyl imidazo[1,2-a]pyridin-5-ylthioacetate and 224 g (1.60 mol) of hexamethylenetetramine in 500 ml of acetic acid was stirred at 90°C for 1 day. This reaction mixture was poured in water and extracted with 2 portions of ethyl acetate. The organic layers were pooled, washed with water, and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The solid residue was rinsed with diethyl ether to provide crude ethyl 5-thia-1,8b-diazaacenaphthylene-4-carboxylate. 35 This crude product was not purified but used as it was in the next reaction.

Blackish purple solid. Yield 193.69 g

To a solution of 193.69 g of the above ethyl 5-thia-1,8b-diazaacenaphthylene-4-carboxylate in 1 l of ethanol was added a solution of 62.9 g (1.57 mol) of sodium hydroxide in 500 ml of water, and the mixture was stirred at room temperature for 0.5 hour. To this reaction mixture was added about 130 ml of concentrated hydrochloric acid with stirring to bring the pH into the range of 4-5 and the resulting precipitate was recovered by filtration and rinsed with ethanol, acetone, and diethyl ether in that order to provide the title compound.

Orange-colored solid. Yield 96.3 g (55%)

¹H-NMR (DMSO-d₆, 200 MHz) δ: 5.97 (1H, dd, J=6.6, 1.2 Hz), 6.57-6.73 (2H, m), 6.88 (1H, s), 7.12 (1H, s).

IR (KBr): 3413, 1632, 1338 cm⁻¹.

2) Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

While 39.11 g (0.1792 mol) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 21.7 g (0.188 mol) of N-hydroxysuccinimide were stirred together in 500 ml of acetonitrile, 36.1 g (0.188 mol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added, and the mixture was stirred at room temperature overnight. To this reaction mixture was added 30.0 ml (0.215 mol) of triethylamine and, then, a solution of 39.1 g (0.179 mol) of 4-amino-1-(3-phenylpropan-1-yl)piperidine in acetonitrile (100 ml)-chloroform (50 ml) was added. The mixture was stirred at room temperature for 1 hour and the resulting orange-colored precipitate was recovered by filtration and rinsed with acetonitrile (yield 55.75 g). This crude product was purified by silica gel column chromatography (ethyl acetate to ethyl acetate/methanol : 4/1~1/1) and recrystallization from chloroform-ethanol to provide

the title compound.

Red crystals. Yield 49.5 g (66%)

m.p. 189.5-191.0°C

¹H-NMR (CDCl₃, 200 MHz) δ: 1.350-1.568 (2H, m), 1.760-

5 2.134 (6H, m), 2.359 (2H, t, J=7.7 Hz), 2.623 (2H, t, J=7.7 Hz), 2.804-2.865 (2H, m), 3.720-3.920 (1H, m), 5.584 (1H, d, J=8.4 Hz), 6.787 (1H, dd, J=1.6, 6.0 Hz), 6.578-6.702 (3H, m), 7.045 (1H, s), 7.156-7.325 (5H, m).

10 IR (KBr): 2995, 1622, 1545, 1479, 1282 cm⁻¹.

Elemental analysis for C₂₄H₂₆N₄OS

Calcd.: C, 68.87; H, 6.26; N, 13.39

Found : C, 68.83; H, 6.39; N, 13.39

Example 142

15 Synthesis of (E)-1-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-3-(5-thia-1,8b-diazaacenaphthylen-4-yl)propen-1-one dihydrochloride

To a solution of 2.541 g (12.441 mM) of 5-thia-1,8b-diazaacenaphthylene-4-methanol in 30 ml of N,N-dimethylformamide was added 6 g of activated manganese dioxide (Aldrich), and the mixture was stirred at room temperature overnight. This reaction mixture was filtered and the filter cake was washed with N,N-dimethylformamide. The filtrate and washes were combined and the solvent was distilled off under reduced pressure. The crude 5-thia-1,8b-diazaacenaphthylene-4-carbaldehyde thus obtained was not purified but used as it was in the next reaction.

30 To a solution of 5.30 g (14.9 mM) of tert-butyl 4-[(dimethoxyphosphoryl)acetyl]piperidine-1-carboxylate in 50 ml of toluene was added 0.55 g (13.7 mM) of a 60% suspension of sodium hydride in liquid paraffin at room temperature, and the mixture was stirred at the prevailing temperature for 2.5 hours. To this reaction mixture was added a solution of the above crude 5-thia-1,8b-diazaacenaphthylene-4-carbaldehyde in 50 ml of

N,N-dimethylformamide at room temperature, and the mixture was stirred at the prevailing temperature for 2 hours. This reaction mixture was poured in water and extracted with 3 portions of ethyl acetate. The 5 organic layers were pooled and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The resulting crude (E)-1-[1-(tert-butoxycarbonyl)piperidin-4-yl]-3-(5-thia-1,8b-diazaacenaphthylen-4-yl)propen-1-one was not purified but used 10 as it was in the next reaction.

To the above crude (E)-1-[1-(tert-butoxycarbonyl)-piperidin-4-yl]-3-(5-thia-1,8b-diazaacenaphthylen-4-yl)propen-1-one was added 5 ml of concentrated hydrochloric acid, and the mixture was stirred at room 15 temperature for 10 minutes. To this reaction mixture was added ethanol, and the resulting precipitate was recovered by filtration and rinsed with ethanol and diethyl ether to provide the title compound.

Orange-colored solid. Yield 2.596 g (54%)
20 ¹H-NMR (CD₃OD-DMSO-d₆, 200 MHz) δ: 1.672-1.881 (2H, m), 2.050-2.123 (2H, m), 3.017-3.158 (3H, m), 3.422 (2H, t d, J=4.0, 13.2 Hz), 6.381 (1H, d, J=15.8 Hz), 6.787 (1H, d, J=7.4 Hz), 6.876 (1H, s), 7.133 (1H, d, J=8.8 Hz), 7.354 (1H, d, J=15.8 Hz), 7.494 (1H, dd, J=7.8, 9.2 Hz), 7.594 (1H, s).
25 IR (Nujol): 3431, 2686, 1680, 1635, 1587, 1215, 1027, 785 cm⁻¹.

2) Synthesis of (E)-1-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-3-(5-thia-1,8b-diazaacenaphthylen-4-yl)propen-1-one
30

A solution of 0.675 g (1.756 mM) of (E)-1-(piperidin-4-yl)-3-(5-thia-1,8b-diazaacenaphthylen-4-yl)propen-1-one dihydrochloride, 0.52 g (2.63 mM) of 1-bromo-3-phenylpropane, and 0.86 ml (6.15 mM) of triethylamine in 30 ml of acetonitrile, and the mixture 35 was refluxed for 1 day. This reaction mixture was

5 poured in aqueous solution of sodium hydrogen carbonate and extracted with 3 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate~ethyl acetate/methanol : 4/1) to provide the title compound.

10 Deep-purple liquid. Yield 0.159 g (21%)

15 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.619-2.110 (8H, m), 2.339-2.526 (3H, m), 2.634 (2H, t, J=7.7 Hz), 2.962 (2H, t d, J=3.2, 11.3 Hz), 5.894 (1H, dd, J=1.8, 6.4 Hz), 6.050 (1H, d, J=15.0 Hz), 6.345 (1H, s), 6.651-6.786 (2H, m), 7.028-7.325 (7H, m).

20 IR (neat): 2941, 1676, 1564, 1498, 1340, 1261, 1144, 1066, 773, 750, 700 cm⁻¹.

25 3) Synthesis of (E)-1-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-3-(5-thia-1,8b-diazaacacenaphthylen-4-yl)propen-1-one dihydrochloride
In 2 ml of methanol was dissolved 0.159 g of (E)-1-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-3-(5-thia-1,8b-diazaacacenaphthylen-4-yl)propen-1-one, followed by addition of a stoichiometric excess of methanolic hydrochloric acid, and the mixture was stirred for 10 minutes. This reaction mixture was concentrated and crystallized from ethanol-diethyl ether to provide the title compound.

30 Orange-colored solid. Yield 0.151 g
¹H-NMR (CD₃OD, 200 MHz) δ: 1.722-1.921 (2H, m), 2.008-2.171 (4H, m), 2.726 (2H, t, J=7.5 Hz), 3.006-3.178 (5H, m), 3.449 (0.4H, br d, J=12.4 Hz), 3.648 (1.6H, br d, J=11.4 Hz), 6.367 (0.8H, d, J=15.4 Hz), 6.420 (0.2H, d, J=15.8 Hz), 6.794 (1H, d, J=7.4 Hz), 6.883 (1H, s), 7.134 (1H, d, J=9.0 Hz), 7.199-7.418 (6H, m), 7.499 (1H, dd, J=7.6, 9.2 Hz), 7.592 (1H, s).

35 IR (Nujol): 2457, 1678, 1635, 1581, 1209, 1126, 1082,

972, 783, 754, 725 cm⁻¹.

Elemental analysis for C₂₆H₂₉Cl₂N₃OS•1.28H₂O

Calcd.: C, 59.42; H, 6.05; N, 8.00

Found : C, 59.05; H, 5.65; N, 7.93

5 Example 143

Synthesis of (E)-5-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-1-(5-thia-1,8b-diazaacenaphthylen-4-yl)-1-penten-3-one dihydrochloride

10 1) Synthesis of (E)-5-(piperidin-4-yl)-1-(5-thia-1,8b-diazaacenaphthylen-4-yl)-1-penten-3-one dihydrochloride

To a solution of 2.234 g (10.938 mM) of 5-thia-1,8b-diazaacenaphthylene-4-methanol in 25 ml of N,N-dimethylformamide was added 6 g of active manganese dioxide, and the mixture was stirred at room temperature overnight. This reaction mixture was filtered and the filter cake was washed with N,N-dimethylformamide. The filtrate and washes were pooled and concentrated to remove the solvent. The resulting crude 5-thia-1,8b-diazaacenaphthylene-4-carbaldehyde was not purified but used as it was in the next reaction.

20 To a solution of 4.77 g (13.1 mM) of tert-butyl 4-[4-(dimethoxyphosphoryl)-3-oxobutyl]piperidine-1-carboxylate in 50 ml of toluene was added 0.48 g (12.0 mM) of a 60% suspension of sodium hydride in liquid paraffin at room temperature, and the mixture was stirred at the prevailing temperature for 2 hours. This reaction mixture was added to a solution of the above crude 5-thia-1,8b-diazaacenaphthylene-4-carbaldehyde in N,N-dimethylformamide (30 ml)-toluene (50 ml) with ice-cooling and the mixture was stirred at the prevailing temperature for 3 hours. This reaction mixture was poured in water and extracted with 3 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄, and the solvent was distilled off under reduced pressure. The residue was

purified by silica gel column chromatography (ethyl acetate to ethyl acetate/methanol : 9/1) to provide crude (E)-5-[1-(tert-butoxycarbonyl)piperidin-4-yl]-1-(5-thia-1,8b-diazaacenaphthylen-4-yl)-1-penten-3-one.

5 This crude product was not purified but used as it was in the next reaction.

To the above crude (E)-5-[1-(tert-butoxycarbonyl)-piperidin-4-yl]-1-(5-thia-1,8b-diazaacenaphthylen-4-yl)-1-penten-3-one was added 5 ml of concentrated hydrochloric acid and the mixture was stirred at room temperature for 15 minutes. To this reaction mixture was added ethanol, followed by stirring, and the resulting precipitate was recovered by filtration and rinsed serially with ethanol and diethyl ether to provide the title compound.

Orange-colored solid. Yield 0.673 g (15%)
¹H-NMR (CD₃OD, 200 MHz) δ: 1.294-1.479 (2H, m), 1.583-1.646 (3H, m), 1.967 (2H, d, J=13.6 Hz), 2.756 (2H, t, J=7.1 Hz), 2.961 (2H, t, J=13.1 Hz), 3.381 (2H, d, J=12.6 Hz), 6.270 (1H, d, J=15.8 Hz), 6.803 (1H, d, J=7.4 Hz), 6.848 (1H, s), 7.138 (1H, d, J=9.2 Hz), 7.296 (1H, d, J=15.8 Hz), 7.507 (1H, dd, J=7.6, 9.0 Hz), 7.588 (1H s).
IR (Nujol): 3413, 2717, 1680, 1635, 1579, 1211, 1074, 972, 792 cm⁻¹.

2) Synthesis of (E)-5-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-1-(5-thia-1,8b-diazaacenaphthylen-4-yl)-1-penten-3-one

A solution of 0.362 g (0.878 mM) of (E)-5-(piperidin-4-yl)-1-(5-thia-1,8b-diazaacenaphthylen-4-yl)-1-penten-3-one dihydrochloride, 0.26 g (1.32 mM) of 1-bromo-3-phenylpropane, and 0.43 ml (3.07 mM) of triethylamine in 30 ml of ethanol was refluxed for 1 day. The reaction mixture was then poured in aqueous solution of sodium hydrogen carbonate and extracted with 3 portions of ethyl acetate. The organic layers

were pooled and dried over $MgSO_4$ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate to ethyl acetate/methanol : 9/1) to provide the
5 title compound.

Dark-purple liquid. Yield 0.281 g (70%)
 1H -NMR ($CDCl_3$, 200 MHz) δ : 1.158-1.366 (2H, m), 1.524-
10 1.987 (9H, m), 2.345 (2H, t, J=7.7 Hz), 2.561 (2H,
t, J=7.7 Hz), 2.617 (2H, t, J=7.7 Hz), 2.913 (2H,
d, J=11.0 Hz), 5.898 (1H, dd, J=1.8, 6.2 Hz),
5.948 (1H, d, J=15.4 Hz), 6.334 (1H, s), 6.649-
6.785 (2H, m), 7.003 (1H, d, J=15.4 Hz), 7.107
(1H, s), 7.127-7.319 (5H, m).
IR (neat): 2923, 1570, 1500, 1342, 1261, 1144, 1076,
15 964, 773, 733, 700 cm^{-1} .

3) Synthesis of (E)-5-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-1-(5-thia-1,8b-diazaacenaphthylen-4-yl)-1-penten-3-one dihydrochloride
In 2 ml of methanol was dissolved 0.281 g (E)-5-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-1-(5-thia-1,8b-diazaacenaphthylen-4-yl)-1-penten-3-one, followed by addition of a stoichiometric excess of methanolic hydrochloric acid, and the mixture was stirred for 10 minutes. This reaction mixture was concentrated and crystallized from ethanol-diethyl ether to provide the
25 title compound.

Orange-colored solid. Yield 0.309 g
 1H -NMR (CD_3OD , 200 MHz) δ : 1.403-1.733 (5H, m), 1.952-
30 2.148 (4H, m), 2.672-2.780 (4H, m), 2.910 (2H, t,
J=12.1 Hz), 3.041-3.125 (2H, m), 3.555 (2H, d,
J=13.2 Hz), 6.254 (1H, d, J=16.2 Hz), 6.791 (1H,
d, J=7.6 Hz), 6.841 (1H, s), 7.130 (1H, d, J=9.2
Hz), 7.171-7.336 (6H, m), 7.496 (1H, dd, J=7.5,
8.9 Hz), 7.579 (1H, s).
35 IR (Nujol): 3408, 3165, 2679, 1668, 1641, 1184, 972,
762, 723 cm^{-1} .

Elemental analysis for C₂₈H₃₃Cl₂N₃OS•1.0H₂O

Calcd.: C, 61.31; H, 6.43; N, 7.66

Found : C, 61.01; H, 6.53; N, 7.58

Example 144

5 Synthesis of (E)-4-[2-[1-(3-phenylpropan-1-yl)piperidin-4-ylmethanesulfonyl]vinyl]-5-thia-1,8b-diazaacenaphthylene dihydrochloride

10 1) Synthesis of (E)-4-[2-(piperidin-4-ylmethanesulfonyl)vinyl]-5-thia-1,8b-

10 diazaacenaphthylene dihydrochloride

To a solution of 0.904 g (4.426 mM) of 5-thia-1,8b-diazaacenaphthylene-4-methanol in 30 ml of N,N-dimethylformamide was added 2 g of activated manganese dioxide (Aldrich), and the mixture was stirred at room temperature for 4 hours. This reaction mixture was filtered and the filter cake was washed with N,N-dimethylformamide. The filtrate and washes were pooled and the solvent was distilled off under reduced pressure. The resulting crude 5-thia-1,8b-diazaacenaphthylene-4-carbaldehyde was not purified but used as it was in the next reaction.

To a solution of 2.01 g (4.87 mM) of tert-butyl 4-(diethoxyphosphorylmethanesulfonylmethyl)piperidine-1-carboxylate in 30 ml of toluene was added 0.18 g (4.43 mM) of a 60% suspension of sodium hydride in liquid paraffin at room temperature, and the mixture was stirred at the prevailing temperature for 1 hour. This reaction mixture was added to a solution of the above crude 5-thia-1,8b-diazaacenaphthylene-4-carbaldehyde in N,N-dimethylformamide (10 ml)-toluene (30 ml) at room temperature and the mixture was stirred at the prevailing temperature for 0.5 hour. This reaction mixture was poured in water and extracted with 3 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was

purified by silica gel column chromatography (ethyl acetate-ethyl acetate/methanol = 9/1) to provide crude (E)-4-[2-[1-(tert-butoxycarbonyl)piperidin-4-ylmethane-sulfonyl]vinyl]-5-thia-1,8b-diazaacenaphthylene. This
5 crude product was not purified but used as it was in the next reaction.

To the above crude (E)-4-[2-[1-(tert-butoxycarbonyl)piperidin-4-ylmethane-sulfonyl]vinyl]-5-thia-1,8b-diazaacenaphthylene was added 3 ml of concentrated hydrochloric acid, and the mixture was stirred at room temperature for 10 minutes. To this reaction mixture was added ethanol, and the resulting precipitate was recovered by filtration and rinsed serially with ethanol and diethyl ether to provide the title
15 compound.

Orange-colored solid. Yield 1.398 g (73%)
¹H-NMR (CD₃OD, 200 MHz) δ: 1.520-1.734 (2H, m), 2.189 (2H, br d, J=15.4 Hz), 2.278-2.410 (1H, m), 3.068 (2H, t, J=12.6 Hz), 3.226 (2H, d, J=6.6 Hz), 3.398 (2H, d, J=12.4 Hz), 6.801 (1H, d, J=7.2 Hz), 6.805 (1H, d, J=15.4 Hz), 6.920 (1H, s), 7.149 (1H, d, J=8.8 Hz), 7.274 (1H, d, J=15.4 Hz), 7.514 (1H, dd, J=7.6, 9.0 Hz), 7.625 (1H, s).
IR (Nujol): 2715, 1633, 1597, 1308, 1201, 1134, 945, 25 854, 785, 737 cm⁻¹.
2) Synthesis of (E)-4-[2-[1-(3-phenylpropan-1-yl)-piperidin-4-ylmethane-sulfonyl]vinyl]-5-thia-1,8b-diazaacenaphthylene

A solution of 0.402 g (0.925 mM) of (E)-4-[2-(piperidin-4-ylmethane-sulfonyl)vinyl]-5-thia-1,8b-diazaacenaphthylene dihydrochloride, 0.28 g (1.39 mM) of 1-bromo-3-phenylpropane, and 0.45 ml (3.24 mM) of triethylamine in 20 ml of ethanol was refluxed for 1 day. This reaction mixture was poured in aqueous 35 solution of sodium hydrogen carbonate and extracted with 2 portions of ethyl acetate. The organic layers

were pooled and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate~ethyl acetate/methanol : 9/1-1/1) to provide
5 the title compound.

Red liquid. Yield 0.373 g (94%)
10 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.681-1.822 (2H, m), 1.887-
2.311 (7H, m), 2.542 (2H, t, J=7.8 Hz), 2.653 (2H,
t, J=7.6 Hz), 2.977 (2H, d, J=6.2 Hz), 3.072-3.182
15 (2H, m), 5.929 (1H, dd, J=1.8, 6.2 Hz), 6.060 (1H,
d, J=15.0 Hz), 6.396 (1H, s), 6.692-6.814 (2H, m),
7.023 (1H, d, J=15.0 Hz), 7.161-7.326 (6H, m).
IR (neat): 2939, 1581, 1498, 1294, 1126, 837, 777, 731
cm⁻¹.

15 3) Synthesis of (E)-4-[2-[1-(3-phenylpropan-1-yl)-
piperidin-4-ylmethanesulfonyl]vinyl]-5-thia-1,8b-
diazaacenaphthylene dihydrochloride

In 2 ml of methanol was dissolved 0.418 g of (E)-
4-[2-[1-(3-phenylpropan-1-yl)piperidin-4-
20 ylmethanesulfonyl]vinyl]-5-thia-1,8b-
diazaacenaphthylene, followed by addition of a
stoichiometric excess of methanolic hydrochloric acid,
and the mixture was stirred for 10 minutes. This
reaction mixture was concentrated and crystallized from
25 ethanol-diethyl ether to provide the title compound.

Orange-colored solid. Yield 0.373 g

1¹H-NMR (CD₃OD, 200 MHz) δ: 1.584-1.799 (2H, m), 2.000-
2.258 (5H, m), 2.711 (2H, t, J=7.5 Hz), 2.962-
3.141 (4H, m), 3.218 (2H, d, J=6.2 Hz), 3.550-
30 3.619 (2H, m), 6.800 (1H, d, J=7.6 Hz), 6.802 (1H,
d, J=15.0 Hz), 6.924 (1H, s), 7.125-7.307 (7H, m),
7.510 (1H, dd, J=7.4, 9.0 Hz), 7.627 (1H, s).

IR (Nujol): 2638-2360, 1633, 1591, 1306, 1269, 1122,
847, 816, 768 cm⁻¹.

35 Elemental analysis for C₂₆H₃₁Cl₂N₃O₂S₂•3.0H₂O

Calcd.: C, 51.48; H, 6.15; N, 6.93

Found : C, 51.69; H, 6.20; N, 6.55

Example 145

Synthesis of (E)-4-[2-[1-(3-phenylpropan-1-yl)piperidin-4-ylmethylthio]vinyl]-5-thia-1,8b-

5 diazaacenaphthylene dihydrochloride

1) Synthesis of (E)-4-[2-(piperidin-4-ylmethylthio)vinyl]-5-thia-1,8b-diazaacenaphthylene dihydrochloride

To a solution of 1.073 g (5.253 mM) of 5-thia-1,8b-diazaacenaphthylene-4-methanol in 30 ml of chloroform was added 3 g of activated manganese dioxide (Aldrich) and the mixture was stirred at room temperature for 4 hours. This reaction mixture was filtered and the filter cake was washed with chloroform. The filtrate and washes were pooled and the solvent was distilled off under reduced pressure. The crude 5-thia-1,8b-diazaacenaphthylene-4-carbaldehyde thus obtained was not purified but used as it was in the next reaction.

20 To a solution of 2.20 g (5.78 mM) of tert-butyl 4-(diethoxyphosphorylmethylthiomethyl)piperidine-1-carboxylate and the above crude 5-thia-1,8b-diazaacenaphthylene-4-carbaldehyde in N,N-dimethylformamide (10 ml)-toluene (50 ml) was added 0.59 g (5.25 mM) of tert-butoxypotassium and the mixture was stirred at room temperature for 15 minutes. This reaction mixture was poured in water and extracted with 3 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄ and the solvent was distilled off under reduced pressure. To the residue was added 4 ml of concentrated hydrochloric acid, and the mixture was stirred at room temperature for 10 minutes. To this reaction mixture was added ethanol, followed by stirring, and the resulting precipitate was recovered by filtration and rinsed serially with ethanol and diethyl ether to provide the title compound.

Yellow solid. Yield 0.667 g (32%)

¹H-NMR (CD₃OD, 200 MHz) δ: 1.409-1.612 (2H, m), 1.859-2.017 (1H, m), 2.098 (2H, d, J=13.6 Hz), 2.894 (2H, d, J=6.2 Hz), 3.004 (2H, t, J=12.4 Hz), 3.418 (2H, d, J=13.2 Hz), 6.318 (1H, d, J=15.4 Hz), 6.321 (1H, s), 6.644 (1H, d, J=15.4 Hz), 6.767 (1H, d, J=7.6 Hz), 7.119 (1H, d, J=9.2 Hz), 7.405 (1H, s), 7.473 (1H, dd, J=7.8, 8.8 Hz).

IR (Nujol): 2706, 1637, 1500, 1207, 937, 773 cm⁻¹.

10 2) Synthesis of (E)-4-[2-[1-(3-phenylpropan-1-yl)-piperidin-4-ylmethylthio]vinyl]-5-thia-1,8b-diazaace-naphthylene

A solution of 0.314 g (0.780 mM) of (E)-4-[2-(piperidin-4-ylmethylthio)vinyl]-5-thia-1,8b-diazaace-naphthylene dihydrochloride, 0.19 g (0.94 mM) of 1-bromo-3-phenylpropane, and 0.38 ml (2.73 mM) of triethylamine in 20 ml of ethanol was refluxed for 1 day. This reaction mixture was poured in aqueous solution of sodium hydrogen carbonate and extracted with 2 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate to ethyl acetate/methanol : 4/1) to provide the title compound.

25 Red liquid. Yield 0.233 g (67%)

¹H-NMR (CDCl₃, 200 MHz) δ: 1.255-1.614 (3H, m), 1.795-2.004 (6H, m), 2.381 (2H, t, J=7.7 Hz), 2.584-2.683 (4H, m), 2.956 (2H, d, 11.6 Hz), 5.862 (1H, dd, J=1.0, 6.8 Hz), 5.891 (1H, s), 5.986 (1H, d, J=15.4 Hz), 6.113 (1H, d, J=15.4 Hz), 6.625 (1H, dd, J=6.8, 9.4 Hz), 6.737 (1H, dd, J=1.1, 9.1 Hz), 6.951 (1H, s), 7.134-7.317 (5H, m).

30 IR (neat): 2933, 1610, 1475, 1290, 1246, 1136, 916, 851, 771, 700 cm⁻¹.

35 3) Synthesis of (E)-4-[2-[1-(3-phenylpropan-1-yl)-

piperidin-4-ylmethylthio]vinyl]-5-thia-1,8b-diazaace-naphthylene dihydrochloride

In 2 ml of methanol was dissolved 0.233 g of (E)-4-[2-[1-(3-phenylpropan-1-yl)piperidin-4-ylmethylthio]-5-thia-1,8b-diazaacenaphthylene, followed by addition of a stoichiometric excess of methanolic hydrochloric acid, and the mixture was stirred for 10 minutes. This reaction mixture was concentrated to provide the title compound.

10 Orange-colored foam. Yield 0.253 g

¹H-NMR (CD₃OD, 200 MHz) δ: 1.504-1.700 (2H, m), 1.840-2.167 (5H, m), 2.713 (2H, t, J=7.1 Hz), 2.882 (2H, d, J=6.6 Hz), 2.969-3.141 (4H, m), 3.552-3.654 (2H, m), 6.312 (1H, d, J=15.4 Hz), 6.321 (1H, s), 6.632 (1H, d, J=15.8 Hz), 6.765 (1H, d, J=7.4 Hz), 7.121 (1H, d, J=9.2 Hz), 7.167-7.340 (5H, m), 7.405 (1H, s), 7.470 (1H, dd, J=7.8, 9.2 Hz). IR (neat): 2949, 2717-2553, 1635, 1574, 1498, 1448, 1304, 1213, 783, 752, 702 cm⁻¹.

20 Elemental analysis for C₂₆H₃₁Cl₂N₃S₂•2.0H₂O

Calcd.: C, 56.10; H, 6.34; N, 7.55

Found : C, 55.99; H, 6.50; N, 7.57

Example 146

Synthesis of (E)-N-[1-(3-phenylpropan-1-yl)piperidin-4-ylmethyl]-2-(5-thia-1,8b-diazaacenaphthylen-4-yl)vinylsulfonamide dihydrochloride

1) Synthesis of (E)-N-(piperidin-4-ylmethyl)-2-(5-thia-1,8b-diazaacenaphthylen-4-yl)vinylsulfonamide dihydrochloride

30 To a solution of 0.800 g (3.917 mM) of 5-thia-1,8b-diazaacenaphthylene-4-methanol in 30 ml of chloroform was added 3 g of activated manganese dioxide (Aldrich) and the mixture was stirred at room temperature for 4 hours. This reaction mixture was filtered and the filter cake was washed with chloroform. The filtrate and washes were pooled and

the solvent was distilled off under reduced pressure. The resulting crude 5-thia-1,8b-diazaacenaphthylene-4-carbaldehyde was not purified but used as it was in the next reaction.

5 To a solution of 2.16 g (4.11 mM) of tert-butyl 4-(diphenoxypyrophosphorylmethanesulfonaminoethyl)-piperidine-1-carboxylate in toluene (20 ml)-tetrahydrofuran (20 ml) was added 0.33 g (8.23 mM) of a 60% suspension of sodium hydride in liquid paraffin at room
10 temperature and the mixture was stirred at the prevailing temperature for 1 hour. This reaction mixture was added to a solution of the above crude 5-thia-1,8b-diazaacenaphthylene-4-carbaldehyde in N,N-dimethylformamide (10 ml)-toluene (50 ml) at room
15 temperature and the mixture was stirred at the prevailing temperature for 0.5 hour. This reaction mixture was poured in water and extracted with 3 portions of ethyl acetate. The organic layers were pooled and dried over MgSO₄ and the solvent was
20 distilled off under reduced pressure. The residue was subjected to silica gel column chromatography (ethyl acetate to ethyl acetate/methanol : 9/1) to provide crude (E)-N-[1-(tert-butoxycarbonyl)piperidin-4-ylmethyl]-2-(5-thia-1,8b-diazaacenaphthylen-4-yl)vinylsulfonamide. To this crude product was added 1 ml of concentrated hydrochloric acid, and the mixture was stirred at room temperature for 30 minutes. To this reaction mixture was added ethanol, followed by stirring, and the resulting precipitate was recovered and washed serially with ethanol and diethyl ether to provide the title compound.
30
35 Yellow solid. Yield 0.384 g (22%)

¹H-NMR (CD₃OD, 200 MHz) δ: 1.339-1.631 (2H, m), 1.727-2.186 (3H, m), 2.910-3.063 (4H, m), 3.360-3.452 (2H, m), 6.546 (1H, d, J=14.8 Hz), 6.809 (1H, d, J=7.6 Hz), 6.840 (1H, s), 7.119 (1H, d, J=14.6

Hz), 7.151 (1H, d, J=9.2 Hz), 7.516 (1H, dd, J=7.6, 9.2 Hz), 7.594 (1H, s).

IR (Nujol): 3064, 2727-2505, 1637, 1601, 1138, 1061, 851, 787 cm⁻¹.

5 2) Synthesis of (E)-N-[1-(3-phenylpropan-1-yl)piperidin-4-ylmethyl]-2-(5-thia-1,8b-diazaacenaphthylen-4-yl)vinylsulfonamide

A solution of 0.285 g (0.634 mM) of (E)-N-(piperidin-4-ylmethyl)-2-(5-thia-1,8b-diazaacenaphthylen-4-yl)vinylsulfonamide dihydrochloride, 0.15 g (0.76 mM) of 1-bromo-3-phenylpropane, and 0.31 ml (2.22 mM) of triethylamine in 20 ml of ethanol was refluxed for 1 day. This reaction mixture was then poured in aqueous solution of sodium hydrogen carbonate and extracted with 2 portions of ethyl acetate. The organic layers were combined and dried over MgSO₄, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate~ethyl acetate/methanol : 9/1) to provide the title compound.

20 Red foam. Yield 0.217 g (69%).

¹H-NMR (CDCl₃, 200 MHz) δ: 1.230-1.623 (3H, m), 1.726-2.036 (6H, m), 2.333-2.496 (2H, m), 2.624 (2H, t, 7.7 Hz), 2.875-3.029 (4H, m), 5.130 (1H, br s), 5.895 (1H, dd, 1.4, 6.6 Hz), 6.003 (1H, d, 15.0 Hz), 6.322 (1H, s), 6.638-6.800 (2H, m), 6.901 (1H, d, 15.0 Hz), 7.120-7.315 (6H, m).

25 IR (neat): 3030, 2931, 1585, 1329, 1140, 731 cm⁻¹.

30 3) Synthesis of (E)-N-[1-(3-phenylpropan-1-yl)piperidin-4-ylmethyl]-2-(5-thia-1,8b-diazaacenaphthylen-4-yl)vinylsulfonamide dihydrochloride

In 2 ml of methanol was dissolved 0.217 g of (E)-N-[1-(3-phenylpropan-1-yl)piperidin-4-ylmethyl]-2-(5-thia-1,8b-diazaacenaphthylen-4-yl)vinylsulfonamide, followed by addition of a stoichiometric excess of

methanolic hydrochloric acid, and the mixture was stirred for 10 minutes. This reaction mixture was concentrated to provide the title compound.

Orange-colored foam. Yield 0.247 g

5 ¹H-NMR (CD₃OD, 200 MHz) δ: 1.434-1.628 (2H, m), 1.714-2.165 (5H, m), 2.709 (2H, t, J=7.5 Hz), 2.911 (2H, d, J=6.6 Hz), 3.008-3.141 (4H, m), 3.522-3.621 (2H, m), 6.536 (1H, d, J=15.4 Hz), 6.803 (1H, d, J=7.2 Hz), 6.838 (1H, s), 7.106 (1H, d, J=15.4 Hz), 7.150 (1H, d, J=9.2 Hz), 7.155-7.332 (5H, m), 7.506 (1H, dd, J=7.8, 9.0 Hz), 7.590 (1H, s).
IR (Nujol): 3351, 2667, 1632, 2331, 1144, 725 cm⁻¹.

Elemental analysis for C₂₆H₃₂Cl₂N₄O₂S₂•1.0H₂O

Calcd.: C, 53.33; H, 5.85; N, 9.57

15 Found : C, 53.24; H, 5.59; N, 9.64

Example 147

Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

1) Synthesis of 5-thia-1,8b-diazaacenaphthylene-4-20 carboxylic acid

To a suspension of 2.2 g of ethyl 5-thia-1,8b-diazaacenaphthylene-4-carboxylate in methanol (6.6 ml) was added 1N-aqueous solution of sodium hydroxide (13 ml), and the mixture was stirred at room temperature for 2 hours. This reaction mixture was adjusted to pH 5 with 1N-hydrochloric acid under ice-cooling. Then, the mixture was stirred at room temperature for 1 hour. The resulting crystal cropwas harvested by filtration and dried to provide 5-thia-1,8b-diazaacenaphthylene-4-30 carboxylic acid (1.8 g, 94%).

¹H-NMR (300 MHz, DMSO-d₆) δ: 5.97 (1H, d, J=7.0 Hz), 6.60 (2H, d, J=9.1 Hz), 6.67 (1H, dd, J=7.0, 9.1 Hz), 6.89 (1H, s), 7.12 (1H, s).

2) Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
35 (i) Process (A)

A suspension of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid (1.2 g), 4-amino-1-(3-phenylpropan-1-yl)piperidine dihydrochloride (1.5 g), triethylamine (1.5 ml), 1-hydroxy-1H-benzotriazole monohydrate (0.8 g), and 1-ethyl-3-(3-diethylaminopropyl)carbodiimide hydrochloride (1.0 g) in N,N-dimethylformamide (15 ml) was stirred at 50°C for 2 hours. After spontaneous cooling, this reaction mixture was extracted with ethyl acetate/tetrahydrofuran (4/1; 90 ml). The organic layer was washed with 1N-aqueous solution of sodium hydroxide (10 ml) and water (30 ml) and concentrated. The resulting crystal crop was rinsed with diisopropyl ether (20 ml) and dried to provide the title compound (2.0 g, 95%).

15 ii) Process (B)

To a suspension of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid (10 g) and N,N-dimethylformamide (1.8 ml) in tetrahydrofuran (100 ml) was added oxalyl chloride (8 ml) dropwise with ice-cooling. Then, at room temperature, the mixture was stirred for 24 hours. This reaction mixture was concentrated and dissolved in N,N-dimethylformamide (40 ml).

25 To a solution of 4-amino-1-(3-phenylpropyl)-piperidine dihydrochloride (13.4 g), 1,8-diazabicyclo-[5.4.0]-7-undecene (13.7 ml), triethylamine (25.6 ml), and N,N-dimethylformamide (60 ml) was added the solution prepared above under ice-cooling using care not to allow the temperature to rise beyond 10°C. The mixture was then stirred at room temperature for 1.5 hours. This reaction mixture was diluted with water (400 ml) and extracted with ethyl acetate/tetrahydrofuran (4/1; 200 ml). The organic layer was washed with 1N-aqueous solution of sodium hydroxide (100 ml) and water (300 ml) and concentrated. The resulting crystals were rinsed with diisopropyl

ether (20 ml) and dried to provide the title compound (12.9 g, 67%).

¹H-NMR (300 MHz, CDCl₃) δ: 1.45-1.53 (2H, m), 1.69-1.83 (2H, m), 1.85-1.92 (2H, m), 1.96-2.08 (2H, m), 5
2.33-2.38 (2H, m), 2.60-2.65 (2H, m), 2.81-2.85 (2H, m), 3.79-3.82 (1H, m), 5.53 (1H, d, J=7.8 Hz), 5.78 (1H, d, J=6.6 Hz), 6.59-6.69 (3H, m), 7.05 (1H, s), 7.16-7.19 (3H, m), 7.25-7.30 (2H, m).

10 Example 148

Synthesis of N-[4-(3-phenylpropan-1-yl)piperazin-1-ylcarbonylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

15 1) Synthesis of N-[4-(3-phenylpropan-1-yl)piperazin-1-ylcarbonylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a suspension of 1.0 g (4.58 mmol.) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 1.05 g (9.12 mmol.) of N-hydroxysuccinimide in acetonitrile 20 (20 ml) was added, at room temperature, 1.76 g (9.18 mmol.) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide·hydrochloride. The mixture was stirred for 1.5 hour. To the reaction system was added a solution of 1.68 g (5.03 mmol.) of 25 1-aminoacetyl-4-(3-phenylpropan-1-yl)piperazine dihydrochloride, 1.53 g (10.05 mmol.) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 0.7 ml (5.02 mmol.) of triethylamine in acetonitrile (15 ml). The mixture was stirred for further 2 hours. The solvent 30 was distilled off under reduced pressure. To the residue was added water. The mixture was subjected to extraction with ethyl acetate (a small volume of ethanol was also used). The organic layer was washed with a saturated aqueous solution of sodium 35 hydrogencarbonate and a saturated aqueous saline solution, which was dried over magnesium sulfate. The

solvent was distilled off under reduced pressure to leave a crude product, which was purified by means of a column chromatography (methanol/ethyl acetate 30-50%) to afford the object compound as a reddish amorphous substance. The yield was 1.32 g (62%).

5 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.71-1.91 (2H, m), 2.31-
2.51 (6H, m), 2.65 (2H, t, J=7.6 Hz), 3.36-3.45
(2H, m), 3.59-3.73 (2H, m), 4.06 (2H, d, J=3.8
Hz), 5.78 (1H, dd, J=6.0 & 1.8 Hz), 6.58-6.72 (3H,
10 m), 6.90-7.00 (1H, m), 7.05 (1H, s), 7.13-7.35
(5H, m).

IR (KBr): 1637, 1622, 1481, 1282, 1238, 1155, 773, 731,
700 cm⁻¹.

15 2) Synthesis of N-[4-(3-phenylpropan-1-yl)piperazin-1-ylcarbonylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 1.306 g (2.83 mmol.) of N-[4-(3-phenylpropan-1-yl)piperazin-1-ylcarbonylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (10 ml) was added, at room temperature, 1.5 ml (18 mmol.) of 12N hydrochloric acid. The mixture was stirred for several minutes, which was concentrated under reduced pressure. To the resulting crystals were added ethanol and diethyl ether. The crystals were collected by filtration, which were washed with ether and diethyl ether to afford the object compound as orange crystals.

The yield was 1.26 g (83%). m.p. 189-196°C (decomp.).

17 ¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.93-2.17 (2H, m),
2.65 (2H, t, J=7.6 Hz), 2.80-3.29 (6H, m), 3.39-
3.68 (2H, m), 3.91-4.48 (4H, m), 6.59 (1H, d,
J=7.0 Hz), 6.96 (1H, d, J=8.4 Hz), 7.17 (1H, s),
7.19-7.36 (6H, m), 7.66 (1H, s), 8.81-8.91 (1H,
m), 11.18-11.45 (1H, m).

19 IR (KBr): 3260, 1667, 1638, 1503 cm⁻¹.

20 Elemental analysis for C₂₅H₂₉N₅O₂SCl₂·1.5H₂O

Calcd.: C, 53.47; H, 5.74; N, 12.47

Found : C, 53.47; H, 5.65; N, 12.46.

Example 149

Synthesis of N-[4-(2-phenethyl)piperazin-1-ylcarbonylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[4-(2-phenethyl)piperazin-1-ylcarbonylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a suspension of 1.0 g (4.58 mmol.) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 1.05 g (9.12 mmol.) of N-hydroxysuccinimide in acetonitrile (20 ml) was added, at room temperature, 1.76 g (9.18 mmol.) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride. The mixture was stirred for 2 hours. To the reaction system was added a solution of 1.76 g (5.50 mmol.) of 1-aminoacetyl-4-(2-phenethyl)piperazine dihydrochloride, 1.67 g (10.97 mmol.) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 0.64 ml (4.59 mmol.) of triethylamine in acetonitrile (15 ml). The mixture was stirred for further one hour. The solvent was distilled off under reduced pressure. To the residue was added water. The mixture was subjected to extraction with ethyl acetate (a small volume of ethanol was also used). The organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous saline solution, which was dried over magnesium sulfate to give a crude product. The crude product was purified by means of a column chromatography (methanol/ethyl acetate 30-40%), followed by crystallization from ethyl acetate to afford the object product as purple crystals. The yield was 1.18 g (57%). m.p. 137-139°C
¹H-NMR (CDCl₃, 200 MHz) δ: 2.46-2.58 (4H, m), 2.58-2.71 (2H, m), 2.75-2.87 (2H, m), 3.38-3.49 (2H, m), 3.63-3.75 (2H, m), 4.07 (2H, d, J=4.0 Hz),

5.78 (1H, dd, J=6.0 & 1.8 Hz), 6.55-6.67 (2H, m),
6.71 (1H, s), 6.92-7.01 (1H, m), 7.05 (1H, s),
7.16-7.36 (5H, m).

5 IR (KBr): 3423, 3255, 1632, 1618, 1556, 1481, 1282,
1246, 1157 cm⁻¹.

2) Synthesis of N-[4-(2-phenethyl)piperazin-1-ylcarbonylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

10 To a solution of 1.13 g (2.52 mmol.) of N-[4-(2-phenethyl)piperazin-1-ylcarbonylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (10 ml) was added, at room temperature, 1.5 ml (18 mmol.) of 12N hydrochloric acid. The mixture was stirred for several minutes. The reaction mixture was concentrated
15 under reduced pressure. To the resulting crystals were added ethanol and diethyl alcohol. The crystals were collected by filtration, followed by washing with ethanol and diethyl ether to give the object compound as orange crystals. The yield was 1.20 g (91%).

20 m.p. 165-175°C (decomp.)

25 ¹H-NMR (DMSO-d₆, 200 MHz) δ: 2.84-3.42 (8H, m), 3.49-3.73 (2H, m), 3.92-4.52 (4H, m), 6.61 (1H, d, J=7.2 Hz), 6.98 (1H, d, J=9.2 Hz), 7.19 (1H, s), 7.20-7.42 (6H, m), 7.68 (1H, s), 8.85-8.96 (1H, m), 11.42-11.72 (1H, m).

IR (KBr): 3260, 1669, 1634 cm⁻¹.

Elemental analysis for C₂₄H₂₇N₅O₂SCl₂·2.0H₂O

Calcd.: C, 51.80; H, 5.61; N, 12.58

Found : C, 51.86; H, 5.34; N, 12.54.

30 Example 150

Synthesis of N-[4-(3-phenylpropan-1-yl)-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-ylcarbonylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

35 1) Synthesis of N-[4-(3-phenylpropan-1-yl)-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-ylcarbonylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a suspension of 1.0 g (4.58 mmol.) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 1.05 g (9.12 mmol.) of N-hydroxysuccinimide in acetonitrile (20 ml) was added, at room temperature, 1.76 g (9.18 mmol.) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride. The mixture was stirred for one hour. To the reaction system was added a solution of 1.91 g (5.48 mmol.) of 1-(aminoacetyl)-4-(3-phenylpropan-1-yl)-2,3,5,6-tetrahydro-7H-1,4-diazepine dihydrochloride, 1.67 g (10.97 mmol.) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 0.7 ml (5.0 mmol.) of triethylamine in acetonitrile (20 ml). The mixture was stirred for further one hour. The solvent was distilled off under reduced pressure. To the residue was added water. The mixture was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous saline solution, followed by drying over magnesium sulfate. The solvent was distilled off under reduced pressure to leave a crude product, which was purified by means of a column chromatography (methanol/ethyl acetate 30-50%) to afford the object compound as an amorphous substance.

The yield was 1.00 g (46%).

¹H-NMR (CDCl₃, 200 MHz) δ: 1.68-1.97 (4H, m), 2.42-2.55 (2H, m), 2.55-2.75 (6H, m), 3.39-3.50 (2H, m), 3.60-3.72 (2H, m), 4.03-4.08 (2H, m), 5.77 (1H, dd, J=6.2 & 1.8 Hz), 6.55-6.65 (2H, m), 6.70 (1H, s), 6.95-7.06 (1H, m), 7.04 (1H, s), 7.13-7.34 (5H, m).

IR (KBr): 3243, 1644, 1622, 1454, 1283, 1157, 772, 702 cm⁻¹.

2) Synthesis of N-[4-(3-phenylpropan-1-yl)-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-ylcarbonylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 1.00 g (2.1 mmol.) of N-[4-(3-phenylpropan-1-yl)-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-ylcarbonylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (10 ml) was added, at room temperature, 1 ml (12 mmol.) of 12N hydrochloric acid. The mixture was stirred for several minutes, followed by concentration under reduced pressure. To the resulting crystals was added diethyl ether. The crystals were collected by filtration, which were washed with ethanol and diethyl ether to give the object product as orange crystals. The yield was 0.996 g (86%).

m.p. 269-275°C (decomp.)

¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.90-2.19 (4H, m), 2.54-2.70 (2H, m), 2.85-3.36 (4H, m), 3.38-3.65 (5H, m), 3.77-4.19 (3H, m), 6.63 (1H, d, J=7.4 Hz), 6.99 (1H, d, J=8.2 Hz), 7.15-7.38 (7H, m), 7.69 (1H, s), 8.83-8.96 (1H, m), 11.04-11.31 (1H, m). IR (KBr): 3268, 1661, 1638, 1501 cm⁻¹.

Elemental analysis for C₂₆H₃₁N₅O₂SCl₂•1.0H₂O

Calcd.: C, 55.12; H, 5.87; N, 12.36

Found : C, 54.82; H, 5.59; N, 12.54.

Example 151

Synthesis of N-[4-(2-phenethyl)-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-ylcarbonylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride
1) Synthesis of N-[4-(2-phenethyl)-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-ylcarbonylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a suspension of 1.0 g (4.58 mmol.) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 1.05 g (9.12 mmol.) of N-hydroxysuccinimide in acetonitrile (20 ml) was added, at room temperature, 1.76 g (9.18 mmol.) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride. The mixture was stirred for one hour. To the reaction

system was added a solution of 1.84 g (5.50 mmol.) of 1-(aminoacetyl)-4-(2-phenethyl)-2,3,5,6-tetrahydro-7H-1,4-diazepine dihydrochloride, 1.68 g (11.0 mmol.) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 0.7 ml (5.0 mmol.) of triethylamine in acetonitrile (20 ml).
5 The mixture was stirred for further one hour. The solvent was distilled off under reduced pressure. To the residue was added water. The mixture was subjected to extraction with ethyl acetate (a small volume of ethanol was also used). The organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous saline solution, which was dried over magnesium sulfate, followed by distilling off the solvent to leave a crude
10 product. The crude product was purified by means of a column chromatography (methanol/ethyl acetate 20-50%) to afford the object compound as a reddish amorphous product. The yield was 0.91 g (43%).
15 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.78-1.99 (2H, m), 2.64-
2.85 (8H, m), 3.40-3.50 (2H, m), 3.61-3.76 (2H, m), 4.01-4.09 (2H, m), 5.78 (1H, dd, J=5.8 & 1.8 Hz), 6.55-6.68 (2H, m), 6.72 (1H, s), 6.96-7.05 (1H, m), 7.05 (1H, s), 7.13-7.34 (5H, m).
20 2) Synthesis of N-[4-(2-phenethyl)-2,3,5,6-tetrahydro-
25 7H-1,4-diazepin-1-ylcarbonylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride
To a solution of 0.91 g (1.97 mmol.) of N-[4-(2-phenethyl)-2,3,5,6-tetrahydro-7H-1,4-diazepin-1-ylcarbonylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-
30 carboxamide in ethanol (10 ml) was added, at room temperature, 1 ml (12 mmol.) of 12N hydrochloric acid. The mixture was stirred for one hour. To the resulting crystals was added diethyl ether, and the crystals were collected by filtration and washed with ethanol and diethyl ether to give the object compound as orange
35 crystals. The yield was 0.9181 g (87%).

m.p. 269-275°C (decomp.)

¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.99-2.23 (2H, m), 2.96-4.21 (14H, m), 6.59 (1H, d, J=7.4 Hz), 6.96 (1H, d, J=9.0 Hz), 7.14-7.41 (7H, m), 7.65 (1H, s), 8.80-8.90 (1H, m), 10.99-11.23 (1H, m).

5 IR (KBr): 3425, 1633, 1566, 1500, 1458, 1296, 1121, 783 cm⁻¹.

Elemental analysis for C₂₅H₂₉N₅O₂SCl₂·1.5H₂O

Calcd.: C, 53.47; H, 5.74; N, 12.47

10 Found : C, 53.37; H, 5.65; N, 12.69.

Example 152

Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-ylaminocarbonylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

15 1) Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-ylaminocarbonylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a suspension of 0.5 g (2.29 mmol.) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 0.53 g (4.61 mmol.) of N-hydroxysuccinimide in acetonitrile (10 ml) was added, at room temperature, 0.88 g (4.59 mmol.) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride. The mixture was stirred for 2 hours. To the reaction system was added a solution of 0.96 g (2.76 mmol.) of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-aminoacetamide dihydrochloride, 0.84 g (5.52 mmol.) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 0.4 ml (2.87 mmol.) of triethylamine in acetonitrile (10 ml). The mixture was stirred for further one hour. The solvent was distilled off under reduced pressure. To the residue was added water, and the mixture was subjected to extraction with chloroform. The organic layer was washed with a saturated aqueous saline solution and dried over magnesium sulfate, followed by distilling off the solvent under reduced pressure to

leave a crude product. The crude product was purified by means of a column chromatography (methanol/ethyl acetate 1:3 ~ 1:1 ~ 3:1), followed by recrystallization from ethyl acetate to afford the object compound as
5 purple crystals. The yield was 303.2 mg (28%).
m.p. 202-205°C

10 $^1\text{H-NMR}$ (CDCl_3 , 200 MHz) δ : 1.36-2.00 (6H, m), 2.00-
2.17 (2H, m), 2.30-2.42 (2H, m), 2.63 (2H, t,
J=7.6 Hz), 2.76-2.92 (2H, m), 3.66-3.87 (1H, m),
3.91 (2H, d, J=4.8 Hz), 5.78 (1H, dd, J=6.0 & 1.8
Hz), 5.80-5.90 (1H, m), 6.56-6.74 (4H, m), 7.05
(1H, s), 7.13-7.33 (5H, m).
IR (KBr): 3281, 3065, 2946, 1649, 1622, 1553, 1483,
1287, 1267, 1159, 775 cm^{-1} .

15 2) Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-ylaminocarbonylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

20 To a solution of 303.2 mg (0.64 mmol.) of N-[1-(3-phenylpropan-1-yl)piperidin-4-ylaminocarbonylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (5 ml) was added, at room temperature, 0.5 ml (6.0 mmol.) of 12N hydrochloric acid. The mixture was stirred for one hour. The mixture was concentrated under reduced pressure. To the concentrate were added 25 ethanol and diethyl ether. The resulting crystals were collected by filtration and washed with ethanol and diethyl ether to afford the object compound as orange crystals. The yield was 257.5 mg (73%).
m.p. 178-183°C decomp.)

30 $^1\text{H-NMR}$ ($\text{DMSO-}c$, 200 MHz) δ : 1.61-2.11 (6H, m), 2.54-
2.71 (2H, m), 2.77-3.87 (9H, m), 6.54 (1H, d,
J=7.4 Hz), 6.93 (1H, d, J=8.8 Hz), 7.09 (1H, s),
7.10-7.36 (6H, m), 7.61 (1H, s), 8.16-8.25 (1H,
m), 8.80-8.95 (1H, m).

35 IR (KBr): 3220, 3059, 1649, 1636, 1566, 1535, 1501,
1298 cm^{-1} .

Elemental analysis for C₂₆H₂₁N₅O₂SCl₂·1.5H₂O

Calcd.: C, 54.26; H, 5.95; N, 12.17

Found : C, 54.01; H, 5.74; N, 12.18.

Example 153

5 Synthesis of N-[4-(4-benzoylpiperazin-1-yl)butan-1-yl]-
5-thia-1,8b-diazaacenaphthylene-4-carboxamide
dihydrochloride

10 1) Synthesis of N-[4-(4-benzoylpiperazin-1-yl)butan-1-
yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

10 To a suspension of 1.0 g (4.58 mmol.) of 5-thia-
1,8b-diazaacenaphthylene-4-carboxylic acid and 1.05 g
(9.12 mmol.) of N-hydroxysuccinimide in acetonitrile
(15 ml) was added, at room temperature, 1.76 g (9.18
mmol.) of N-ethyl-N'-3-(N,N-

15 dimethylamino)propylcarbodiimide hydrochloride. The
mixture was stirred for 2 hours. To the reaction
system was added a solution of 1.68 g (5.5 mmol.) of 4-
(4-aminobutan-1-yl)-1-benzoylpiperazine
dihydrochloride, 1.68 g (11.04 mmol.) of 1,8-

20 diazabicyclo[5.4.0]undecene (DBU) and 1.5 ml (10.76
mmol.) of triethylamine in acetonitrile (10 ml). The
mixture was stirred for further 2 hours. The solvent
was distilled off under reduced pressure. To the

25 residue was added water, which was subjected to
extraction with ethyl acetate (a small volume of
ethanol was also used). The organic layer was washed
with a saturated aqueous saline solution and dried over
magnesium sulfate, followed by distilling off the
solvent. The residue was purified by means of a column
30 chromatography (methanol/ethyl acetate 20 - 30%) to
give the object compound as a reddish amorphous
product. The yield was 1.25 g (59%).

35 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.42-1.63 (4H, m), 2.24-
2.56 (6H, m), 3.19-3.55 (4H, m), 3.63-3.88 (2H,
m), 5.76-5.80 (1H, m), 5.96-6.08 (1H, m), 6.55-
6.69 (3H, m), 7.02 (1H, s), 7.34-7.45 (5H, m).

IR (KBr): 3309, 1616, 1547, 1437, 1281, 1155, 1012, 775, 733, 712 cm⁻¹.

2) Synthesis of N-[4-(4-benzoylpiperazin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 1.16 g (2.51 mmol.) of N-[4-(4-benzoylpiperazin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol was added, at room temperature, 1 ml (12 mmol.) of 12N hydrochloric acid. The mixture was stirred for several minutes. The resulting crystals were collected by filtration and washed with ethanol and diethyl ether to give the object compound as orange crystals. The yield was 0.918 g (69%).

m.p. 247-253°C (decomp.)

¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.40-1.58 (2H, m), 1.62-1.84 (2H, m), 2.96-3.24 (8H, m), 3.31-3.64 (4H, m), 6.61 (1H, d, J=6.8 Hz), 6.97 (1H, d, J=8.6 Hz), 7.22 (1H, s), 7.28 (1H, dd, J=7.6 & 9.2 Hz), 7.42-7.55 (5H, m), 7.64 (1H, s), 8.85-8.97 (1H, m).

IR (KBr): 3398, 1632, 1568, 1533, 1500, 1429, 1288 cm⁻¹.

Elemental analysis for C₂₅H₂₉N₅O₂SCl₂·1.5H₂O

Calcd.: C, 53.47; H, 5.74; N, 12.47

Found : C, 53.28; H, 5.74; N, 12.73.

Example 154

Synthesis of N-[3-(4-benzoylpiperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[3-(4-benzoylpiperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a suspension of 0.8 g (3.67 mmol.) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 0.84 g (8.8 mmol.) of N-hydroxysuccinimide in acetonitrile (15 ml) was added, at room temperature, 1.41 g (7.36 mmol.)

of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride. The mixture was stirred for 2 hours. To the reaction system was added a solution of 1.41 g (4.4 mmol.) of 4-(3-aminopropan-1-yl)-1-
5 benzoylpiperazin dihydrochloride, 1.34 g (8.8 mmol.) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1.0 ml (7.17 mmol.) of triethylamine in acetonitrile (15 ml). The mixture was stirred for further 2 hours. The solvent was distilled off under reduced pressure. To
10 the residue was added water, which was subjected to extraction with ethyl acetate (a small volume of ethanol was also used). The organic layer was washed with a saturated aqueous saline solution, dried over magnesium sulfate and subjected to distillation
15 under reduced pressure. The residue was subjected to fractional purification by means of a column chromatography (methanol/ethyl acetate 30-40%), followed by distilling off the solvent under reduced pressure to afford the object compound as a reddish
20 purple crystalline product. The yield was 0.738 g (45%).

¹H-NMR (CDCl₃, 200 MHz) δ: 1.68-1.81(2H,m), 2.43-
2.63 (6H, m), 3.37-3.49 (2H, m), 3.55-3.92 (4H,
m), 5.77 (1H, dd, J=1.8 & 6.6 Hz), 6.60-6.69 (1H,
m), 6.73 (1H, s), 7.05 (1H, s), 7.25-7.35 (1H, m),
25 7.35-7.47 (5H, m).

IR (KBr): 3319, 1612, 1545, 1444, 1273, 1153 cm⁻¹.
2) Synthesis of N-[3-(4-benzoylpiperazin-1-yl)propan-1-
30 yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
dihydrochloride

To a solution of 0.715 g (1.60 mmol.) of N-[3-(4-benzoylpiperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (10 ml) was added, at room temperature, 10 ml (120 mmol.) of 12N
35 hydrochloric acid. The mixture was stirred for 16 hours, which was concentrated under reduced pressure.

To the concentrate were added ethanol and diethyl ether. The resulting crystals were collected by filtration and washed with ethanol and diethyl ether to give the object compound as orange crystals. The 5 yield was 0.715 g (86%).

m.p. 277-282°C (decomp.)

¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.82-2.01 (2H, m), 2.96-3.28 (8H, m), 3.34-3.61 (4H, m), 6.55 (1H, d, J=7.8 Hz), 6.93 (1H, d, J=9.2 Hz), 7.13 (1H, s), 10 7.18-7.26 (1H, m), 7.41-7.51 (5H, m), 7.60 (1H, s), 8.84-8.96 (1H, m).

IR (KBr): 3344, 1632, 1529, 1423, 1302, 800 cm⁻¹.

Elemental analysis for C₂₄H₂₇N₅O₂SCl₂·1.5H₂O

Calcd.: C, 52.65; H, 5.52; N, 12.79

15 Found : C, 52.95; H, 5.30; N, 12.95.

Example 155

Synthesis of N-cis-[4-(4-benzyl-3,5-dimethylpiperazin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride

20 1) Synthesis of N-cis-[4-(1-benzyl-2,6-dimethylpiperazin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a suspension of 1.0 g (4.58 mmol.) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 1.05 g (9.12 mmol.) of N-hydroxysuccinimide in acetonitrile (15 ml) was added, at room temperature, 1.76 g (9.18 mmol.) of N-ethyl-N'-3-(N,N-dimethylamino)propyl carbodiimide hydrochloride. The mixture was stirred for 2 hours. To the reaction system was added a solution of 1.64 g (5.95 mmol.) of cis-4-(1-benzyl-2,6-dimethylpiperazin-1-yl)butan-1-ylamine and 1.5 ml (10.76 mmol.) of triethylamine in acetonitrile (15 ml). The mixture was stirred for further 2 hours. The solvent was distilled off under reduced pressure. To 30 the residue was added water, which was subjected to extraction with chloroform. The organic layer was

washed with a saturated aqueous saline solution and dried over magnesium sulfate. The solvent was distilled off under reduced pressure to leave a crude product, which was subjected to fractional purification
5 by means of a column chromatography (methanol/ethyl acetate 30%) to afford the object compound as a reddish amorphous product. The yield was 1.55 g (91%).

10 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.05 (6H, d, J=6.0 Hz),
 1.47-1.63 (4H, m), 1.73-1.93 (2H, m), 2.24-2.36 (2H,
 m), 2.61-2.82 (4H, m), 3.23-3.36 (2H, m), 3.83 (2H, m),
 5.74 (1H, dd, J=6.2 & 1.8 Hz), 6.56 (1H, s), 6.57-6.69
 (3H, m), 6.97 (1H, s), 7.13-7.39 (5H, m).
15 IR (KBr): 3319, 1618, 1549, 1479, 1281, 1153, 773, 729
 cm⁻¹.

2) Synthesis of N-cis-[4-(1-benzyl-2,6-dimethylpiperazin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride
To a solution of 1.55 g (3.21 mmol.) of N-cis-[4-(1-benzyl-2,6-dimethylpiperazin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (10 ml) was added 3.0 ml (36 mmol.) of 12N hydrochloric acid. The mixture was stirred for several minutes. The solvent was distilled off under reduced pressure.
20 The residue was added 2-propanol. The resulting crystals were collected by filtration and washed with 2-propanol and diethyl ether to give the object compound as orange crystals. The yield was 1.274 g (67%).
25 To the residue was added 2-propanol. The resulting crystals were collected by filtration and washed with 2-propanol and diethyl ether to give the object compound as orange crystals. The yield was 1.274 g (67%).

30 ¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.35-1.84 (10H, m), 3.00-3.45 (6H, m), 3.56-3.84 (4H, m), 4.42-4.64 (2H, m), 6.62 (1H, d, J=7.4 Hz), 6.98 (1H, d, J=9.2 Hz), 7.22 (1H, s), 7.29 (1H, dd, J=9.2 & 7.6 Hz), 7.38-7.62 (5H, m), 7.65 (1H, s), 8.82-8.95 (1H, m).
35 IR (KBr): 3423, 1635, 1537, 1498, 1448, 1296, 1215,

783, 746 cm⁻¹.

Elemental analysis for C₂₇H₃₆N₅OSCl₃•1.0H₂O

Calcd.: C, 53.78; H, 6.39; N, 11.61

Found : C, 53.54; H, 6.39; N, 11.48.

5 Example 156

Synthesis of N-cis-[3-(4-benzyl-3,5-dimethylpiperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride

10 1) Synthesis of N-cis-[3-(4-benzyl-3,5-dimethylpiperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a suspension of 1.0 g (4.58 mmol.) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 1.05 g (9.12 mmol.) of N-hydroxysuccinimide in acetonitrile (30 ml) was added, at room temperature, 1.76 g (9.18 mmol.) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride. The mixture was stirred for 2 hours. To the reaction system was added a solution of 1.56 g (5.97 mmol.) of cis-4-(3-aminopropyl)-1-benzyl-2,6-dimethylpiperazine and 2.0 ml (14.3 mmol.) of triethylamine in acetonitrile (15 ml). The mixture was stirred for further one hour. The solvent was distilled off under reduced pressure. To the residue was added water, which was subjected to extraction with chloroform. The organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous saline solution, which was dried over magnesium sulfate. Then, the solvent was distilled off under reduced pressure to leave a crude product, which was subjected to fractional purification by means of a column chromatography (methanol/ethyl acetate 30%) to afford the object compound as a reddish amorphous product. The yield was 1.00 g (48%).

35 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.03 (6H, d, J=6.2 Hz),
1.58-1.79 (2H, m), 1.83-1.94 (2H, m), 2.45-2.50

(2H, m), 2.62-2.93 (4H, m), 3.32-3.45 (2H, m),
3.77 (2H, s), 5.69 (1H, dd, J=6.2 & 1.8 Hz), 6.55-
6.67 (3H, m), 6.98 (1H, s), 7.13-7.42 (5H, m),
8.03-8.14 (1H, m).

5 IR (KBr): 3283, 2960, 2810, 1618, 1543, 1479, 1279,
1151, 729 cm⁻¹.

2) Synthesis of N-cis-[3-(4-benzyl-3,5-dimethylpiperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride

10 To a solution of 1.00 g (2.17 mmol.) of N-cis-[3-(4-benzyl-3,5-dimethylpiperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (10 ml) was added 2.0 ml (36 mmol.) of 12N hydrochloric acid. The mixture was stirred for one hour. The solvent was distilled off under reduced pressure. To the residue were added 2-propanol and diethyl ether. The resulting crystals were collected by filtration and washed with 2-propanol and diethyl ether to afford the object compound as orange crystals. The yield was

20 0.8489 g (69%).

¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.41-1.70 (6H, m), 1.78-
1.98 (2H, m), 2.97-3.43 (6H, m), 3.55-3.82 (4H,
m), 4.42-4.62 (2H, m), 6.61 (1H, d, J=7.4 Hz),
6.98 (1H, d, J=8.8 Hz), 7.19 (1H, s), 7.28 (1H,
dd, J=9.2 & 7.2 Hz), 7.41-7.63 (5H, m), 7.66 (1H,
s), 8.92-9.04 (1H, m).

IR (KBr): 3435, 3390, 1633, 1566, 1535, 1500, 1452,
1390, 1298, 1213, 785 cm⁻¹.

Elemental analysis for C₂₆H₃₄N₅OSCl₃·1.5H₂O

30 Calcd.: C, 52.22; H, 6.24; N, 11.71

Found : C, 52.41; H, 6.40; N, 11.59.

Example 157

Synthesis of N-cis-[2-[4-(3-phenylpropan-1-yl)-3,5-dimethylpiperazin-1-yl]ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride

35 1) Synthesis of N-cis-[2-[4-(3-phenylpropan-1-yl)-3,5-

dimethylpiperazin-1-yl]ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a suspension of 1.0 g (4.58 mmol.) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 1.05 g (9.12 mmol.) of N-hydroxysuccinimide in acetonitrile (15 ml) was added 1.76 g (9.18 mmol.) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride. The mixture was stirred for 2 hours. To the reaction system was added a solution of 1.89 g (6.86 mmol.) of cis-1-(2-aminoethyl)-4-(3-phenylpropan-1-yl)-3,5-dimethylpiperazine and 2.0 ml (14.3 mmol.) of triethylamine in acetonitrile (15 ml). The mixture was stirred for 2 hours. The solvent was distilled off under reduced pressure. To the residue was added water, which was subjected to extraction with chloroform. The organic layer was washed with a saturated aqueous saline solution, which was dried over magnesium sulfate. The solvent was distilled off under reduced pressure to leave a crude product, which was purified by a column chromatography (methanol/ethyl acetate 30%) to afford the object compound as a reddish amorphous product. The yield was 1.33 g (61%).
¹H-NMR (CDCl₃, 200 MHz) δ: 1.03 (6H, d, J=5.8 Hz), 1.63-2.01 (4H, m), 2.44 (2H, t, J=5.6 Hz), 2.55 (2H, t, J=7.6 Hz), 2.61-2.88 (6H, m), 3.28-3.42 (2H, m), 5.74 (1H, dd, J=6.4 & 1.6 Hz), 6.40-6.49 (1H, m), 6.52-6.69 (3H, m), 7.03 (1H, s), 7.13-7.35 (5H, m).
IR (KBr): 3325, 2939, 2812, 1618, 1547, 1483, 1281, 1153, 773, 733, 700 cm⁻¹.
2) Synthesis of N-cis-[2-[4-(3-phenylpropan-1-yl)-3,5-dimethylpiperazin-1-yl]ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride
To a solution of 1.32 g (2.78 mmol.) of N-cis-[2-[4-(3-phenylpropan-1-yl)-3,5-dimethylpiperazin-1-yl]ethan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (10 ml) was added 2.0 ml (24

mmol.) of 12N hydrochloric acid. The mixture was stirred for one hour. The resulting crystals were collected by filtration, and washed with ethanol and diethyl ether to give the object compound as an orange
5 crystalline product. The yield was 1.41 g (87%).

¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.32 (6H, d, J=5.8 Hz),
1.79-2.04 (2H, m), 2.64-2.76 (2H, m), 3.07-3.39
(6H, m), 3.48-3.62 (2H, m), 3.72-4.06 (4H, m),
6.61 (1H, d, J=7.2 Hz), 6.96 (1H, d, J=9.2 Hz),
10 7.17-7.40 (7H, m), 7.64 (1H, s), 9.02-9.15 (1H,
m).

IR (KBr): 2419, 2426, 2637, 1566, 1498, 1444, 1290,
1213 cm⁻¹.

Elemental analysis for C₂₇H₃₆N₅OSCl,
15 Calcd.: C, 55.43; H, 6.20; N, 11.97
Found : C, 55.39; H, 6.23; N, 11.97.

Example 158

Synthesis of N-trans-[4-(4-benzyl-2,5-dimethylpiperazin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride
20 1) Synthesis of N-trans-[4-(4-benzyl-2,5-dimethylpiperazin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a suspension of 1.0 g (4.58 mmol.) of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid and 1.05 g (9.12 mmol.) of N-hydroxysuccinimide in acetonitrile (15 ml) was added, at room temperature, 1.76 g (9.18 mmol.) of N-ethyl-N'-3-(N,N-dimethylamino)propylcarbodiimide hydrochloride. The
25 mixture was stirred for 2 hours. To the reaction system was added a solution of 1.64 g (5.95 mmol.) of trans-1-(4-aminobutyl)-4-benzyl-2,5-dimethyl-piperazine and 2.0 ml (14.3 mmol.) of triethylamine in acetonitrile (15 ml). The mixture was stirred for
30 further 2 hours. The solvent was distilled off under reduced pressure. To the residue was added water, and
35

the mixture was subjected to extraction with chloroform. The organic layer was washed with a saturated aqueous saline solution, which was dried over magnesium sulfate, followed by distilling off the solvent to leave a crude product. The crude product was purified by means of a column chromatography (methanol/ethyl acetate 30%) to afford the object compound as a reddish amorphous product. The yield was 1.797 g (83%).

10 ¹H-NMR (CDCl₃, 200 MHz) δ: 0.97 (3H, d, J=6.2 Hz), 1.17 (3H, d, J=5.8 Hz), 1.47-1.63 (4H, m), 1.83-2.52 (4H, m), 2.61 (1H, dd, J=11.0 & 2.8 Hz), 2.71-2.80 (1H, m), 2.84 (1H, dd, J=11.4 & 3.0 Hz), 3.05 (1H, d, J=13.2 Hz), 3.24-3.37 (2H, m), 4.09 (1H, d, J=13.2 Hz), 5.77 (1H, dd, J=6.4 & 1.8 Hz), 6.21-6.33 (1H, m), 6.57-6.70 (3H, m), 7.03 (1H, s), 7.17-7.36 (5H, m).

15 IR (KBr): 3325, 3253, 2935, 2800, 1618, 1547, 1279, 1151, 734 cm⁻¹.

20 2) Synthesis of N-trans-[4-(4-benzyl-2,5-dimethyl-piperazin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride
To a solution of 1.65 g (3.47 mmol.) of N-trans-[4-(4-benzyl-2,5-dimethyl-piperazin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (10 ml) was added 2.0 ml (24 mmol.) of 12N hydrochloric acid. The mixture was stirred for one hour. The solvent was distilled off under reduced pressure. To the residue was added 2-propanol. The resulting crystalline precipitate was collected by filtration and washed with 2-propanol and diethyl ether to give the object compound as an orange crystalline product. The yield was 1.844 g (91%).

25 ¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.30 (3H, d, J=5.6 Hz), 1.43-1.78 (7H, m), 2.93-3.90 (10H, m), 4.03-4.28 (1H, m), 4.55-4.73 (1H, m), 6.60 (1H, d, J=7.4

Hz), 6.96 (1H, d, J=8.8 Hz), 7.13-7.32 (2H, m),
7.39-7.50 (3H, m), 7.56-7.69 (3H, m), 8.77-8.92
(1H, m).

IR (KBr): 3453, 3223, 2611, 2463, 2353, 1633, 1497,
5 1443, 1298, 777, 746 cm⁻¹.

Elemental analysis for C₂₇H₃₆N₅OSCl,

Calcd.: C, 55.43; H, 6.20; N, 11.97

Found : C, 55.37; H, 6.23; N, 11.96

Example 159

10 Synthesis of N-[2-(2,6-dioxo-4-(3-phenylpropan-1-
y1)piperazin-1-yl)ethan-1-yl]-5-thia-1,8b-
diazaacenaphthylene-4-carboxamide dihydrochloride
1) Synthesis of N-[2-(2,6-dioxo-4-(3-phenylpropan-1-
y1)piperazin-1-yl)ethan-1-yl]-5-thia-1,8b-
15 diazaacenaphthylene-4-carboxamide

To a suspension of 0.8 g (3.67 mmol.) of ethyl 5-
thia-1,8b-diazaacenaphthylene-4-carboxylate and 0.84 g
(7.30 mmol.) of N-hydroxysuccinimide in acetonitrile
(10 ml) was added, at room temperature, 1.41 g (7.36
20 mmol.) of N-ethyl-N'-3-(N,N-
dimethylamino)propylcarbodiimide. The mixture was
stirred for 2 hours. To the reaction system was added
a solution of 1.66 g (4.77 mmol.) of 1-(2-aminoethan-
1-y1)-2,6-dioxo-4-(3-phenylpropan-1-yl)pi-
25 perazine.dihydrochloride and 2.7 ml (19.4 mmol.) of
triethylamine in chloroform (5 ml). The mixture was
stirred for further one hour. The solvent was
distilled off under reduced pressure. To the residue
was added water, and the mixture was subjected to
30 extraction with chloroform. The organic layer was
washed with a saturated aqueous saline solution, which
was dried over magnesium sulfate. The concentrate was
purified by means of a column chromatography
(methanol/ethyl acetate 20%) to afford the object
35 compound as a reddish amorphous product. The yield was
1.56 g (89%).

- 5 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.72-1.92 (2H, m), 2.40-
2.54 (2H, m), 2.60-2.73 (2H, m), 3.24-3.59 (6H,
m), 3.97-4.06 (2H, m), 5.73 (1H, dd, J=6.2 & 1.4
Hz), 6.23-6.35 (1H, m), 6.54-6.66 (3H, m), 7.01
(1H, s), 7.11-7.35 (5H, m).
- 10 IR (KBr): 3350, 2941, 1736, 1682, 1620, 1545, 1346,
1279, 1234, 1182, 1151, 748, 700, 644 cm⁻¹.
- 15 2) Synthesis of N-[2-(2,6-dioxo-4-(3-phenylpropan-1-
yl)piperazin-1-yl)ethan-1-yl]-5-thia-1,8b-
10 diazaacenaphthylene-4-carboxamide dihydrochloride
- 15 To a solution of 1.56 g (3.28 mmol.) of N-[2-(2,6-
dioxo-4-(3-phenylpropan-1-yl)piperazin-1-yl)ethan-1-
yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in
ethanol (10 ml) was added, at room temperature, 2 ml
15 (24 mmol.) of 12N hydrochloric acid. The mixture was
stirred for several minutes, which was concentrated
under reduced pressure to leave crystals. To the
crystals was added ethanol, which was subjected to
filtration to collect the crystals. The crystals was
20 washed with ethanol and diethyl ether to give the
object compound as an orange crystalline product. The
yield was 1.20 g (66%).
- 25 ¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.87-2.08 (2H, m), 2.61-
2.68 (2H, m), 2.96-3.13 (2H, m), 3.20-3.36 (2H,
m), 3.72-3.85 (2H, m), 4.13 (4H, br s), 6.64 (1H,
d, J=7.2 Hz), 6.97 (1H, d, J=9.2 Hz), 7.12 (1H,
s), 7.14-7.37 (6H, m), 7.64 (1H, s), 8.81-8.92
(1H, m).
- 30 IR (KBr): 3260, 2952, 2590, 1745, 1697, 1633, 1562,
1529, 1500, 1438, 1345, 1293, 1212, 780, 630 cm⁻¹.
- 35 Elemental analysis for C₂₅H₂₇N₅O₃SCl₂•2.0H₂O
Calcd.: C, 51.37; H, 5.35; N, 11.98
Found : C, 51.69; H, 5.28; N, 12.05.
- Example 160
- 35 Synthesis of N-[1-[3-(4-ethoxycarbonylphenoxy)propan-1-
yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-

carboxamide dihydrochloride

1) **Synthesis of N-[1-{3-(4-ethoxycarbonylphenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide**

5 To a solution of 0.80 g (2.14 mmol.) of N-(piperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride, 1.5 ml (10.76 mmol.) of triethylamine and 0.38 g of sodium iodide in ethanol (20 ml) was added, at room temperature, 0.62 g (2.55
10 mmol.) of ethyl 4-(3-chloro-1-propoxy)benzoate. The mixture was heated under reflux for two days under nitrogen atmosphere. The reaction mixture was cooled to room temperature, to which was added water, followed by subjecting to extraction with ethyl acetate. The
15 organic layer was washed with a saturated aqueous saline solution, dried over magnesium sulfate, and concentrated. The concentrate was purified by means of a column chromatography (methanol/ethyl acetate 20-40%) to give the object compound as a reddish solid product
20 (758.4 mg, 75%). The product was recrystallized from ethanol to afford the object compound as reddish crystals.

25 ¹H-NMR (CDCl₃, 200 MHz) δ: 1.38 (3H, t, J=7.2 Hz), 1.37-1.55 (2H, m), 1.87-2.03 (4H, m), 2.06-2.22 (2H, m), 2.49-2.56 (2H, m), 2.79-2.94 (2H, m), 3.74-3.94 (1H, m), 4.07 (2H, t, J=6.2 Hz), 4.35 (2H, q, J=7.2 Hz), 5.47-5.58 (1H, m), 5.80 (1H, dd, J=6.2 & 1.6 Hz), 6.59-6.71 (3H, m), 6.91 (2H, d, J=8.8 Hz), 7.07 (1H, s), 7.99 (2H, d, J=8.8 Hz).

30 IR (KBr): 3280, 2945, 1706, 1608, 1536, 1511, 1482, 1280, 1257, 1172, 1056, 954, 883, 844, 771 cm⁻¹.

35 2) **Synthesis of N-[1-{3-(4-ethoxycarbonylphenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride**

To a solution of 329.7 mg (0.65 mmol.) of N-[1-[3-(4-ethoxycarbonylphenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (5 ml) was added, at room temperature, 2 ml (24 mmol.) of 12N hydrochloric acid. The mixture was stirred for one hour. The resulting crystalline precipitate was collected by filtration, followed by washing with ethanol and diethyl ether to afford the object compound (369.8 mg, 98%) as orange crystals.

10 m.p. 162-166°C.

¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.31 (6H, t, J=7.0 Hz), 1.83-2.10 (4H, m), 2.15-2.32 (2H, m), 2.89-3.24 (4H, m), 3.44-3.60 (2H, m), 3.74-3.96 (1H, m), 4.08-4.21 (2H, m), 4.28 (2H, q, J=7.0 Hz), 6.58 (1H, d, J=7.4 Hz), 6.95 (1H, d, J=8.8 Hz), 7.05 (2H, d, J=9.2 Hz), 7.20-7.29 (2H, m), 7.62 (1H, s), 7.92 (2H, d, J=9.2 Hz), 8.79-8.87 (1H, m).
IR (KBr): 3265, 2945, 2636, 1697, 1633, 1605, 1534, 1511, 1255, 1216, 1170, 1128, 1112, 852, 771 cm⁻¹.
20 Elemental analysis for C₂₇H₃₂N₄O₄SCl₂·2.0H₂O
Calcd.: C, 52.68; H, 5.89; N, 9.10
Found : C, 52.96; H, 5.68; N, 8.94.

Example 161

Synthesis of N-[1-[3-(3-ethoxycarbonylphenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[1-[3-(3-ethoxycarbonylphenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

30 To a solution of 0.80 g (2.14 mmol.) of N-(piperidin-1-yl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride, 1.5 ml (10.76 mmol.) of triethylamine and 0.38 g of sodium iodide in ethanol (20 ml) was added, at room temperature, 0.62 g (2.55 mmol.) of ethyl 4-(3-chloro-1-propoxy)benzoate. The mixture was heated under reflux for 2 days under

nitrogen atmosphere. The reaction mixture was cooled to room temperature. To the reaction system was then added water, which was subjected to extraction with ethyl acetate. The organic layer was washed with a
5 saturated aqueous saline solution, which was dried over magnesium sulfate, followed by concentration. The concentrate was purified by means of a column chromatography (methanol/ethyl acetate 30-40%) to afford the object compound (636.2 mg, 59%) as red
10 crystals.

¹H-NMR (CDCl₃, 200 MHz) δ: 1.40 (3H, t, J=7.2 Hz),
1.41-1.58 (2H, m), 1.88-2.04 (4H, m), 2.06-2.21
(2H, m), 2.49-2.56 (2H, m), 2.80-2.94 (2H, m),
3.73-3.94 (1H, m), 4.01 (2H, t, J=6.2 Hz), 4.38
15 (2H, q, J=7.2 Hz), 5.57 (1H, d, J=8.2 Hz), 5.80
(1H, dd, J=6.2 & 1.6 Hz), 6.59-6.71 (3H, m), 7.06
(1H, s), 7.04-7.12 (1H, m), 7.30-7.38 (1H, m),
7.53-7.67 (2H, m).

IR (KBr): 3275, 2952, 1720, 1610, 1540, 1278, 1232,
20 1162, 873, 771 cm⁻¹.

2) Synthesis of N-[1-[3-(3-ethoxycarbonylphenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

25 To a solution of 473.3 mg (0.93 mmol.) of N-[1-[3-(3-ethoxycarbonylphenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (5 ml) was added, at room temperature, 2 ml (24 mmol.) of 12N hydrochloric acid. The mixture was stirred for
30 several minutes. The reaction mixture was concentrated under reduced pressure. To the concentrate was added ethanol. The resulting crystals were collected by filtration and washed with ethanol and diethyl ether to give the object compound (425.4 mg, 79%) as orange
35 crystals, m.p.140-145°C.

¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.32 (3H, t, J=7.0 Hz),

1.84-2.08 (4H, m), 2.14-2.31 (2H, m), 2.94-3.28
(4H, m), 3.47-3.61 (2H, m), 3.79-3.96 (1H, m),
4.08-4.20 (2H, m), 4.31 (2H, q, J=7.0 Hz), 6.59
(1H, d, J=7.4 Hz), 6.96 (1H, d, J=8.4 Hz), 7.18-
5 7.30 (3H, m), 7.42-7.63 (4H, m), 8.85 (1H, d,
J=7.2 Hz).

IR (KBr): 3370, 3053, 2607, 1699, 1635, 1565, 1540,
1444, 1290, 1233, 1203, 1124, 813, 751 cm⁻¹.

Elemental analysis for C₂₇H₃₂N₄O₄SCl₂•2.0H₂O

10 Calcd.: C, 52.68; H, 5.89; N, 9.10
Found : C, 52.80; H, 5.76; N, 9.17.

Example 162

Synthesis of N-[1-[3-(2-methoxycarbonylphenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[1-[3-(2-methoxycarbonylphenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

To a solution of 0.80 g (2.14 mmol.) of N-(piperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride, 1.5 ml (10.76 mmol.) of triethylamine and 0.65 g (4.27 mmol.) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile (20 ml) were added, at room temperature, 0.38 g of sodium iodide and 0.59 g (2.58 mmol.) of methyl 2-(3-chloro-1-propoxy)benzoate. The mixture was heated under reflux for 3 days under nitrogen atmosphere. The solvent was distilled off under reduced pressure. To the residue was added water, which was subjected to extraction with chloroform. The organic layer was washed with a saturated aqueous saline solution, which was dried over magnesium sulfate, followed by concentration. The concentrate was purified by means of a column chromatography (methanol/ethyl acetate 30-50%), followed by distilling off the solvent under reduced pressure to afford the object compound (0.81 g,

77%) as a reddish amorphous product.

¹H-NMR (CDCl₃, 200 MHz) δ: 1.37-1.61 (2H, m), 1.87-2.23 (4H, m), 2.57 (2H, t, J=7.4 Hz), 2.80-2.95 (2H, m), 3.89 (3H, s), 4.09 (2H, t, J=6.2 Hz), 5.51-5.62 (1H, m), 5.80 (1H, dd, J=6.2 & 1.8 Hz), 6.59-6.71 (3H, m), 6.94-7.02 (2H, m), 7.05 (1H, s), 7.40-7.49 (1H, m), 7.76-7.80 (1H, m).

IR (KBr): 3230, 2949, 1727, 1617, 1540, 1482, 1454, 1286, 1249, 1151, 1085, 772, 757 cm⁻¹.

10 2) Synthesis of N-[1-[3-(2-methoxycarbonylphenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To a solution of 0.81 g (1.64 mmol.) of N-[1-[3-(2-methoxycarbonylphenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide in ethanol (5 ml) was added, at room temperature, 1 ml (12 mmol.) of 12N hydrochloric acid. The mixture was stirred for several minutes. The reaction mixture was concentrated, to which was added acetonitrile. The resulting crystalline precipitate was collected by filtration, which was washed with ethanol and diethyl ether to give the object compound (809.1 mg, 87%) as orange crystals, m.p. 164-168°C.

25 ¹H-NMR (DMSO-d₆, 200 MHz) δ: 1.82-2.07 (4H, m), 2.15-2.32 (2H, m), 2.94-3.26 (4H, m), 3.43-3.58 (2H, m), 3.78-3.99 (1H, m), 3.83 (3H, s), 4.10-4.20 (2H, m), 6.60 (1H, d, J=7.4 Hz), 6.95-7.07 (2H, m), 7.14-7.32 (3H, m), 7.50-7.71 (3H, m), 8.87 (1H, d, J=6.8 Hz).

IR (KBr): 3159, 2643, 1687, 1629, 1314, 1247, 764 cm⁻¹.

Elemental analysis for C₂₆H₃₀N₄O₄SCl₂·0.5H₂O

Calcd.: C, 54.36; H, 5.44; N, 9.75

Found : C, 54.30; H, 5.72; N, 9.80.

35 Example 163

2-[3-[4-(5-thia-1,8b-diazaacenaphthylene-4-

carbonylamino)piperidin-1-yl]propan-1-yloxy]benzoic acid dihydrochloride

N-[1-[3-(2-methoxycarbonylphenoxy)-propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide (400 mg) was

5 mixed with 6N hydrochloric acid (20 ml). The mixture was stirred for 2.5 hours at 80°C. The solvent was distilled off under reduced pressure. The resulting crystals were collected by filtration and washed with isopropyl ether to give the object compound (379 mg,

10 97%), m.p. 180-183°C.

¹H-NMR (DMSO-d₆, 200 MHz) δ: 10.70-10.40 (1H, br s), 8.89 (1H, d, J=7.4 Hz), 7.75-7.60 (2H, m), 7.60-7.40 (1H, m), 7.40-7.20 (2H, m), 7.20-6.90 (3H, m), 6.64 (1H, d, J=7.4 Hz), 4.20-2.80 (9H, m), 2.40-1.80 (6H, m).

IR (KBr) ν: 3000, 1695, 1635, 1538, 1496, 1436, 1394, 1230, 1087, 1016, 753 cm⁻¹.

Elemental analysis for C₂₃H₂₈N₄O₄SCl₂•3.5H₂O

Calcd.: C, 48.86; H, 5.74; N, 9.12

20 Found : C, 48.62; H, 5.51; N, 9.13.

Example 164

3-[3-[4-(5-thia-1,8b-diazaacenaphthylene-4-carbonylamino)piperidin-1-yl]propan-1-yloxy]benzoic acid dihydrochloride

25 N-[1-[3-(3-ethoxycarbonylphenoxy)-propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide (400 mg) was

mixed with 6N hydrochloric acid. The mixture was stirred for 4 hours at 80°C. The resulting crystals were collected by filtration and washed with water to

30 give the object compound (255 mg). The filtrate was concentrated under reduced pressure. The resulting crystals were collected by filtration and washed with isopropyl ether to give an additional object compound (122 mg) (total 377 mg, 87%), m.p. 224-230°C.

35 ¹H-NMR (DMSO-d₆, 200 MHz) δ: 8.90-8.75 (1H, m), 7.64-7.36 (4H, m), 7.30-7.15 (2H, m), 6.95 (1H, d,

J=9.2 Hz), 6.58 (1H, d, J=7.8 Hz), 4.29-3.00 (9H, m), 2.35-2.10 (2H, m), 2.10-1.80 (4H, m).

IR (KBr) ν : 3000, 1706, 1635, 1565, 1538, 1500, 1448, 1388, 1212, 1112, 952, 786, 763 cm⁻¹.

5 Elemental analysis for C₂₅H₂₈N₄O₄SCl₂·4.5H₂O

Calcd.: C, 47.47; H, 5.90; N, 8.86

Found : C, 47.39; H, 5.62; N, 9.10.

Example 165

10 4-[3-[4-(5-thia-1,8b-diazaacenaphthylene-4-carbonylamino)piperidin-1-yl]propan-1-yloxy]benzoic acid dihydrochloride

15 N-[1-[3-(4-ethoxycarbonylphenoxy)-propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide (400 mg) was mixed with 6N hydrochloric acid (20 ml). The mixture was stirred for 5 hours at 80°C. The resulting crystals were collected by filtration and washed with water to give the object compound (397 mg, 91%), m.p. 277-280°C.

20 ¹H-NMR (DMSO-d₆, 200 MHz) δ : 7.90 (2H, d, J=8.8 Hz), 7.58 (1H, s), 7.15-7.26 (2H, m), 7.03 (2H, d, J=8.8 Hz), 6.92 (1H, d, J=9.6 Hz), 6.53 (1H, d, J=8.0 Hz), 4.05-4.20 (1H, m), 3.15-4.00 (8H, m), 2.10-2.30 (2H, m), 1.80-2.00 (4H, m).

25 IR (KBr) ν : 3051, 1683, 1633, 1606, 1569, 1502, 1440, 1316, 1259, 1212, 1168, 773 cm⁻¹.

Elemental analysis for C₂₅H₂₈N₄O₄SCl₂·4.0H₂O

Calcd.: C, 48.16; H, 5.82; N, 8.99

Found : C, 48.18; H, 5.73; N, 9.08.

30 Example 166

N-[1-[3-(2-cyanophenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

35 1) N-[1-[3-(2-cyanophenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
2-(3-Chloropropan-1-yl)oxybenzonitrile (503 mg)

was added, at room temperature, to an acetonitrile solution (20 ml) of N-(piperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride (800 mg), 1,8-diazabicyclo[5.4.0]-7-undecene (662 mg), triethylamine (1.09 g) and sodium iodide (285 mg). The mixture was heated under reflux for 7.5 hours under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure. To the concentrate was added water, which was subjected to extraction with chloroform. The extract solution was washed with a saturated aqueous saline solution, which was dried over anhydrous magnesium sulfate, followed by concentration under reduced pressure. The concentrate was purified by means of a silica gel column chromatography (ethyl acetate/methanol=2/1) to afford the object compound (816 mg, 83%) as a reddish purple oily product.

¹H-NMR (CDCl₃, 200 MHz) δ: 7.55 (2H, d, J=8.0 Hz), 7.06-6.95 (3H, m), 6.78 (1H, s), 6.63 (1H, d, J=5.8 Hz), 6.10-5.80 (1H, m), 5.78 (1H, dd, J=1.8 & 5.8 Hz), 4.16 (2H, t, J=6.0 Hz), 4.00-3.80 (1H, m), 3.60-3.40 (2H, m), 3.10-2.90 (2H, m), 2.83-2.65 (2H, m), 2.20-1.90 (6H, m), 1.85-1.60 (2H, m).

2) N-[1-[3-(2-cyanophenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

To an ethanol solution (8.0 ml) of N-[1-[3-(2-cyanophenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide (565 mg) was added conc. hydrochloric acid (3.0 ml). The mixture was stirred for 15 minutes at room temperature. The resulting crystals were collected by filtration and washed with ethanol to give the object compound (462 mg, 70%), m.p. 234-240°C.

¹H-NMR (DMSO-d₆, 200 MHz) δ: 8.90-8.78 (1H, m), 7.80-

7.58 (3H, m), 7.34-7.06 (4H, m), 6.96 (1H, d, J=8.8 Hz), 6.59 (1H, d, J=7.2 Hz), 4.40-4.20 (2H, m), 4.00-2.80 (7H, m), 2.40-2.20 (2H, m), 2.20-1.80 (4H, m).

5 IR (KBr) ν : 3290, 3031, 2638, 2225, 1644, 1633, 1569, 1540, 1498, 1450, 1291, 1263, 1218, 1112, 796 cm^{-1} .

Elemental analysis for $C_{23}H_{27}N_5O_2SCl_2 \cdot 2.0H_2O$

Calcd.: C, 52.82; H, 5.50; N, 12.32

Found : C, 52.89; H, 5.24; N, 12.29

10 Example 167

N-[1-[3-(3-Cyanophenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

15 1) N-[1-[3-(3-Cyanophenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
3-(3-Chloropropan-1-yl)oxybenzonitrile (503 mg) was added, at room temperature, to an acetonitrile solution (20 ml) of N-(piperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride (800 mg), 1,8b-diazabicyclo[5.4.0]-7-undecene (662 mg), triethylamine (1.09 g) and sodium iodide (285 mg). The mixture was heated under reflux for 6.5 hours under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure. To the concentrate was added water, which was subjected to extraction with chloroform. The extract solution was washed with a saturated aqueous saline solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The concentrate was purified by means of a silica gel chromatography (ethyl acetate/methanol=2/1) to afford the object compound (565 mg, 57%) as reddish purple crystals.

30 $^1\text{H-NMR}$ (CDCl_3 , 200 MHz) δ : 7.48-7.00 (4H, m), 6.80-6.58 (3H, m), 5.90-5.70 (2H, m), 4.04 (2H, t, J=6.1 Hz), 3.95-3.70 (1H, m), 3.00-2.81 (2H, m), 2.55 (2H, t, J=7.0 Hz), 2.30-1.80 (6H, m), 1.70-

1.40 (2H, m).

2) N-[1-{3-(3-cyanophenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

5 To an ethanol solution (8.0 ml) of N-[1-{3-(3-cyanophenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide (565 mg) was added conc. hydrochloric acid. The mixture was stirred for 15 minutes at room temperature. The resulting crystals
10 were collected by filtration and washed with ethanol (4622 mg, 70%), m.p. 169-172°C.

15 ¹H-NMR (DMSO-d₆, 200 MHz) δ: 8.90-8.80 (1H, m), 7.62-7.39 (4H, m), 7.38-7.18 (3H, m), 6.95 (1H, d, J=8.6 Hz), 6.58 (1H, d, J=7.2 Hz), 4.20-4.10 (2H, m), 4.00-2.90 (7H, m), 2.20-2.10 (2H, m), 2.10-1.80 (4H, m).

IR (KBr) ν: 3224, 3055, 2549, 2227, 1635, 1565, 1502, 1432, 1317, 1301, 1264, 1214, 784 cm⁻¹.

Elemental analysis for C₂₅H₂₇N₃O₂SCl₂·2.0H₂O

20 Calcd.: C, 52.82; H, 5.50; N, 12.32
Found.: C, 52.92; H, 5.34; N, 12.28.

Example 168

N-[1-{3-(4-Cyanophenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

25 dihydrochloride
1) 4-(3-Chloropropan-1-yl)oxybenzonitrile (503 mg) was added, at room temperature, to an acetonitrile solution (20 ml) of N-(piperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride (800 mg), 1,8-diazabicyclo[5.4.0]-7-undecene (662 mg), triethylamine (1.09 g) and sodium iodide (285 mg). The mixture was heated under reflux for 19 hours under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure. To the
30 concentrate was added water, and the mixture was subjected to extraction with chloroform. The extract
35

solution was washed with a saturated aqueous saline solution, which was dried over anhydrous magnesium sulfate, followed by concentration under reduced pressure. The concentrate was purified by means of a 5 silica gel chromatography (ethyl acetate/methanol=2/1) to afford the object compound (733 mg, 74%) as a reddish purple crystals.

¹H-NMR (CDCl₃, 200 MHz) δ: 7.58 (2H, d, J=8.8 Hz), 7.05 (1H, s), 6.94 (2H, d, J=8.8 Hz), 6.96-6.58 10 (3H, m), 5.88-5.74 (1H, m), 5.79 (1H, dd, J=1.8 & 6.2 Hz), 4.07 (2H, t, J=5.8 Hz), 4.00-3.75 (1H, m), 3.05-2.90 (2H, m), 2.61 (2H, t, J=7.0 Hz), 2.35-1.90 (6H, m), 1.80-1.50 (2H, m).
2) N-[1-[3-(4-Cyanophenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

Conc. hydrochloric acid (3.0 ml) was added to an ethanol solution (8.0 ml) of N-[1-[3-(2-cyanophenoxy)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide (621 mg). The mixture was stirred for 15 minutes at room temperature. The resulting crystals were collected by filtration and washed with ethanol to give the object compound (572 mg, 79%), m.p. 268-272°C.

¹H-NMR (DMSO-d₆, 200 MHz) δ: 8.86 (1H, d, J=7.8 Hz), 7.78 (2H, d, J=9.2 Hz), 7.68-7.58 (1H, m), 7.34-7.18 (2H, m), 7.11 (2H, d, J=9.2 Hz), 6.97 (1H, d, J=8.0 Hz), 6.60 (1H, d, J=7.6 Hz), 4.30-4.10 (2H, m), 4.00-2.94 (7H, m), 2.40-2.15 (2H, m), 2.15-1.80 (4H, m).

IR (KBr) ν: 3212, 3055, 2219, 1631, 1604, 1569, 1538, 1506, 1297, 1263, 1168, 1126, 834, 792 cm⁻¹.

Elemental analysis for C₂₅H₂₇N₅O₂SCl₂·0.8H₂O
Calcd.: C, 54.90; H, 5.27; N, 12.81
35 Found : C, 54.91; H, 5.06; N, 12.96.

Example 169

Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

Oxalyl chloride (4.00 ml) was added dropwise to a suspension of 5-thia-1,8b-diazaacenaphthylene-4-

5 carboxylic acid (5.00 g), tetrahydrofuran (40 ml) and dimethylformamide (0.89 ml) for 10 minutes with cooling with ice. This was stirred for 2 hours at room temperature. The reaction solution was concentrated (concentrated material). Triethylamine (19.8 ml) was
10 added dropwise to a suspension of 4-amino-1-(3-phenylpropyl)piperidine dihydrochloride (7.34 g) and dimethylformamide (20 ml). Insoluble materials were filtered out from the reaction mixture which was stirred for 30 minutes (amine solution). The amine
15 solution was added dropwise to a suspension of the concentrated material and dimethylformamide (20 ml) for 1 hour at 50°C (inner temperature), and then the reaction mixture was stirred for 1 hour at 50°C (inner temperature). The reaction mixture which was added
20 water (200 ml) and 1N-sodium hydroxide (20 ml) was extracted by ethyl acetate:tetrahydrofuran = 4:1 (100 ml x 3). The organic layer was washed with three times of 1N-sodium hydroxide (50 ml) and water (150 ml). Ethyl acetate:isopropyl ether = 1:1 (20 ml) was added
25 into the residual crystal obtained by concentrating the organic layer, and the mixture was stirred for 2 hours at room temperature, and then filtered. The residue was dried under reduced pressure to obtain N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-
30 diazaacenaphthylene-4-carboxamide (7.45 g, 77.7%).
¹H-NMR (CDCl₃, 300MHz, 2H) δ: 1.45-1.50 (m, 2H), 1.77-
1.85 (m, 2H), 1.91-1.95 (d, J=12.68 Hz, 2H), 2.04-
2.11 (t, J=9.62 Hz, 2H), 2.33-2.38(t, J=7.89 Hz,
2H), 2.60-2.65 (t, J=7.79 Hz, 2H), 2.81-2.85 (d,
35 J=11.94 Hz, 2H), 3.79-3.81 (m, 1H), 5.68-5.70 (d,
J=7.73 Hz, 1H), 5.76-5.78 (m, 1H), 6.58-6.68 (m,

3H), 7.03 (s, 1H), 7.16-7.20 (m, 3H), 7.25-7.30 (m, 2H).

Example 170

Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
5 Triethylamine (6.7 ml) was added dropwise to a suspension of 4-amino-1-(3-phenylpropyl)piperidine dihydrochloride (7.01 g) and dimethylformamide (40 ml). The mixture was stirred for 10 minutes. 5-Thia-1,8b-diazaacenaphthylene-4-carboxylic acid (5.00 g), 1-hydroxy-1H-benzotriazole monohydrate (0.710 g) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (4.61 g) were added into the reaction mixture. This was stirred for 2 hours at 68-70°C (inner temperature). Ethyl acetate:tetrahydrofuran = 4:1 (380 ml), 1N-sodium hydroxide (50 ml) and water (80 ml) were added into the reaction solution. The aqueous layer was extracted by ethyl acetate:tetrahydrofuran = 4:1 (120 ml x 2). The organic layer was washed with water (130 ml x 3), and then concentrated. The residue which was added ethyl acetate (15 ml) was stirred for 2 hours at room temperature. The reaction mixture was dried under reduced pressure to obtain N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide (8.87 g, 92.5%).

¹H-NMR (CDCl₃, 300 MHz) δ: 1.45-1.50 (m, 2H), 1.77-1.85 (m, 2H), 1.91-1.95 (d, J=12.68 Hz, 2H), 2.04-2.11 (t, J=9.62 Hz, 2H), 2.33-2.38 (t, J=7.89 Hz, 2H), 2.60-2.65 (t, J=7.79 Hz, 2H), 2.81-2.85 (d, J=11.94 Hz, 2H), 3.79-3.81 (m, 1H), 5.68-5.70 (d, J=7.73 Hz, 1H), 5.76-5.78 (m, 1H), 6.58-6.68 (m, 3H), 7.03 (s, 1H), 7.16-7.20 (m, 3H), 7.25-7.30 (m, 2H).

Example 171

Synthesis of N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

Triethylamine (1.34 ml) was added dropwise to a suspension of 4-amino-1-(3-phenylpropyl)piperidine dihydrochloride (1.40 g) and dimethylformamide (10 ml). Into the mixture which was stirred for 10 minutes, 5-
5 thia-1,8b-diazaacenaphthylene-4-carboxylic acid (1.00 g) and diethyl cyanophosphonate (0.81 ml) were added. The mixture was stirred for 1 hour at room temperature, and 2 hours at 55°C. Ethyl acetate:tetrahydrofuran = 4:1 (1.75 ml) and 1N-sodium hydroxide (30 ml) were
10 added into the reaction mixture. The organic layer which was washed with sodium hydroxide (30 ml x 3) and water (30 ml x 2) was concentrated. The residual crystal which was added ethyl (4 ml) was stirred for 1 hour at room temperature. This was dried under reduced pressure to obtain N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide (1.07 g, 63.6 %).
15 ¹H-NMR (CDCl₃, 300 MHz) δ: 1.45-1.50 (m, 2H), 1.77-1.85 (m, 2H), 1.91-1.95 (d, J=12.68 Hz, 2H), 2.04-2.11 (t,
J=9.62 Hz, 2H), 2.33-2.38 (t, J=7.89 Hz, 2H), 2.60-2.65 (t, J=7.79 Hz, 2H), 2.81-2.85 (d, J=11.94 Hz, 2H),
20 3.79-3.81 (m, 1H), 6.58-6.68 (m, 3H), 7.03 (s, 1H), 7.16-7.20 (m, 3H), 7.25-7.30 (m, 2H).

Example 172

25 Synthesis of N-[3-(4-Phenylmethyl-2-oxopiperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride
1) Synthesis of N-[3-(4-tert-Butoxycarbonyl-2-oxopiperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
30 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.22 g, 22.0 mmol) was added to a stirred suspension of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid (2.40 g, 11.0 mmol) and N-hydroxysuccinimide (2.53 g, 22.0 mmol) in acetonitrile (30 ml) at room temperature and the mixture was stirred
35

at room temperature for 1.5 hours. A solution of 1-(3-aminopropan-1-yl)-4-tert-butoxycarbonyl-2-oxopiperazine (3.67 g, 14.3 mmol) and triethylamine (4.45 g, 44.0 mmol) in acetonitrile (15 ml) was added to the mixture.

5 After stirring at room temperature for 19 hours, the reaction mixture was concentrated in vacuo. The residue was dissolved in water and extracted with chloroform. The extract was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was

10 chromatographed on silica gel (50 g) with Ethyl acetate-Methanol (10:1) to give N-[3-(4-tert-butoxycarbonyl-2-oxopiperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as a purple amorphous powder(1.53 g, 30%).

15 ¹H-NMR (200 MHz, CDCl₃) δ: 7.45-7.30 (1H, m), 7.03 (1H, s), 6.70-6.55 (3H, m), 5.75 (1H, dd, J=6.0 and 1.8 Hz), 4.13 (2H, s), 3.75-3.60 (2H, m), 3.60-3.40 (2H, m), 3.40-3.30 (2H, m), 3.30-3.15 (2H, m), 1.85-1.60 (2H, m), 1.48 (9H, s).

20 IR (KBr) : 3269, 2977, 2931, 1695, 1644, 1482, 1419, 1284, 1164 cm⁻¹.

2) Synthesis of N-[3-(2-Oxopiperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

25 Concentrated hydrochloric acid (4.0 ml) was added to N-[3-(4-tert-butoxycarbonyl-2-oxopiperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide (1.53 g, 3.34 mmol) and the mixture was stirred at room temperature for 30 minutes. The

30 reaction mixture was concentrated in vacuo to give N-[3-(2-oxopiperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as an orange amorphous powder(1.53 g, quant.).

35 ¹H-NMR (200 MHz, DMSO-d₆) δ: 10.00-9.60 (1H, m), 8.85-8.70 (1H, m), 7.68 (1H, s), 7.36-7.25 (1H, m), 7.14 (1H, s), 6.99 (1H, d, J=8.6 Hz), 6.65 (1H, d,

J=7.4 Hz), 4.00-2.80 (6H, m), 2.40-2.10 (2H, m),
1.80-1.55 (4H, m).

3) Synthesis of N-[3-(4-Phenylmethyl-2-oxopiperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

Benzylchloride (187 mg, 1.48 mmol) was added to a stirred solution of N-[3-(2-oxopiperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride (518 mg, 1.20 mmol), triethylamine (605 mg, 5.98 mmol), sodium iodide (216 mg, 1.44 mmol) and 1,8-diazabicyclo[5.4.0]undecene (366 mg, 2.41 mmol) in acetonitrile (20 ml) at room temperature. After refluxing under nitrogen for 2 days, the reaction mixture was concentrated in vacuo. The residue was dissolved in water and extracted with chloroform. The extract was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was chromatographed on silica gel (20 g) with Ethyl acetate-Methanol (8:1) to give N-[3-(4-phenylmethyl-2-oxopiperazine-1-yl)propane-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as a purple amorphous powder (303 mg, 56%).

¹H-NMR (200 MHz, CDCl₃) δ: 7.62-7.45 (1H, m), 7.40-7.20 (5H, m), 7.00 (1H, s), 6.65 (1H, s), 6.60-6.50 (2H, m), 5.73 (1H, dd, J=5.6 and 2.4 Hz), 3.58 (2H, s), 3.52-3.38 (2H, m), 3.38-3.10 (4H, m), 3.20 (2H, s), 2.70 (2H, t, J=5.2 Hz), 1.80-1.60 (2H, m).

IR (KBr) : 3242, 2937, 1627, 1505, 1482, 1282, 1156, 913, 734 cm⁻¹.

4) Synthesis of N-[3-(4-Phenylmethyl-2-oxopiperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

Concentrated hydrochloric acid(0.8 ml) was added to a stirred solution of N-[3-(4-phenylmethyl-2-oxopiperazin-1-yl)propan-1-yl]-5-thia-1,8b-

diazaacenaphthylene-4-carboxamide (300 mg, 0.670 mmol) in ethanol (5.0 ml) at room temperature. After stirring at room temperature for 1 hour, the reaction mixture was concentrated in vacuo to give N-[3-(4-phenylmethyl-2-oxopiperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as an orange amorphous powder (345 mg, 98%).

5 $^1\text{H-NMR}$ (200 MHz, DMSO-d₆) δ: 8.80-8.60 (1H, m), 7.80-7.40 (6H, m), 7.40-7.15 (1H, m), 7.05 (1H, s), 6.95 (1H, d, J=8.4 Hz), 6.56 (1H, d, J=6.6 Hz), 4.38 (2H, s), 4.00-3.20 (8H, m), 3.20-3.00 (2H, m), 1.80-1.50 (2H, m).

10 IR (KBr) : 3240, 3058, 2941, 1635, 1565, 1538, 1502, 1293, 1214, 759, 705 cm⁻¹.

15 Elemental analysis for C₂₄H₂₂Cl₂N₅O₂S•2.5H₂O
Calcd.: C, 50.97; H, 5.70; N, 12.38.
Found : C, 50.90; H, 5.71; N, 12.08.

Example 173

20 Synthesis of N-[3-[4-(2-Phenylethan-1-yl)-2-oxopiperazin-1-yl]propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

25 1) Synthesis of N-[3-[4-(2-Phenylethan-1-yl)-2-oxopiperazin-1-yl]propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
(2-Bromoethyl)benzene (312 mg, 1.68 mmol) was added to a stirred solution of N-[3-(2-oxopiperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride (610 mg, 1.42 mmol), triethylamine (722 mg, 7.13 mmol), sodium iodide (255 mg, 1.70 mmol) and 1,8-diazabicyclo[5.4.0]undecene (438 mg, 2.88 mmol) in acetonitrile (20 ml) at room temperature. After refluxing under nitrogen for 2 days, the reaction mixture was concentrated in vacuo. The residue was dissolved in water and extracted with chloroform. The extract was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was

chromatographed on silica gel(20 g) with Ethyl acetate-Methanol (8:1) to give N-[3-[4-(2-phenylethan-1-yl)-2-oxopiperazin-1-yl]propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as a purple amorphous powder (288 mg, 44%).

¹H-NMR (200 MHz, CDCl₃) δ: 7.65-7.45 (1H, m), 7.40-7.15 (5H, m), 7.01 (1H, s), 6.60-6.50 (2H, m), 5.74 (1H, dd, J=6.0 and 2.2 Hz), 3.60-3.40 (2H, m), 3.40-3.00 (6H, m), 3.00-2.60 (6H, m), 1.80-1.60 (2H, m).

IR (KBr) : 3286, 2935, 1714, 1635, 1506, 1482, 1282, 1156, 732 cm⁻¹.

2) Synthesis of N-[3-[4-(2-Phenylethan-1-yl)-2-oxopiperazin-1-yl]propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

Concentrated hydrochloric acid (0.8 ml) was added to a stirred solution of N-[3-[4-(2-phenylethan-1-yl)-2-oxopiperazin-1-yl]propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide (369 mg, 0.799 mmol) in ethanol (5.0 ml) at room temperature. After stirring at room temperature for 1 hour, the reaction mixture was concentrated in vacuo to give N-[3-[4-(2-phenylethan-1-yl)-2-oxopiperazin-1-yl]propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as an orange amorphous powder (424 mg, 99%).

¹H-NMR (200 MHz, DMSO-d₆) δ: 8.80-8.65 (1H, m), 7.62 (1H, s), 7.60-7.20 (6H, m), 7.08 (1H, s), 7.00-6.90 (1H, m), 6.62-6.50 (1H, m), 4.20-3.20 (10H, m), 3.20-3.00 (4H, m), 1.85-1.55 (2H, m).

IR (KBr) : 3242, 2935, 1652, 1635, 1565, 1538, 1500, 1455, 1361, 1293, 1214, 784, 703 cm⁻¹.

Elemental analysis for C₂₅H₂₉Cl₂N₅O₂S•0.7C₂H₅OH•2.0H₂O
Calcd.: C, 52.60; H, 6.22; N, 11.62.
Found : C, 52.74; H, 5.96; N, 11.68.

Example 174

Synthesis of N-[3-[4-(3-Phenylpropan-1-yl)-2-oxopiperazin-1-yl]propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[3-[4-(3-Phenylpropan-1-yl)-2-

5 oxopiperazin-1-yl]propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

1-Bromo-3-phenylpropane (210 mg, 1.05 mmol) was added to a stirred solution of N-[3-(2-oxopiperazin-1-yl)propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride (389 mg, 0.904 mmol), triethylamine (459 mg, 4.53 mmol), sodium iodide (163 mg, 1.09 mmol) and 1,8-diazabicyclo[5.4.0]undecene (275 mg, 1.81 mmol) in acetonitrile (10 ml) at room temperature. After refluxing under nitrogen for 2 days, the reaction mixture was concentrated in vacuo. The residue was dissolved in water and extracted with chloroform. The extract was washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (15 g) with Ethyl acetate-Methanol (8:1) to give N-[3-[4-(3-phenylpropan-1-yl)-2-oxopiperazin-1-yl]propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as a purple amorphous powder (285 mg, 66%).

¹H-NMR (200 MHz, CDCl₃) δ: 7.62-7.50 (1H, m), 7.40-7.15

25 (5H, m), 7.01 (1H, s), 6.66 (1H, s), 6.62-6.50 (2H, m), 5.74 (1H, dd, J=6.0 and 2.2 Hz), 3.54-3.40 (1H, m), 3.36-3.26 (2H, m), 3.26-3.12 (2H, m), 3.18 (2H, s), 2.67 (4H, t, J=7.4 Hz), 1.95-1.40 (4H, m).

30 IR (KBr) : 3294, 2935, 1714, 1635, 1506, 1282, 1156, 732 cm⁻¹.

2) Synthesis of N-[3-[4-(3-Phenylpropan-1-yl)-2-oxopiperazin-1-yl]propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

35 Concentrated hydrochloric acid (0.8 ml) was added to a stirred solution of N-[3-[4-(3-phenylpropan-1-yl)-

2-oxopiperazin-1-yl]propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide (261 mg, 0.549 mmol) in ethanol (5.0 ml) at room temperature. After stirring at room temperature for 1 hour, the reaction mixture was concentrated in vacuo to give N-[3-(3-phenylpropan-1-yl)-2-oxopiperazin-1-yl]propan-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as an orange amorphous powder (295 mg, 98%).

10 ¹H-NMR (200 MHz, DMSO-d₆) δ: 8.82-8.70 (1H, m), 7.67 (1H, s), 7.40-7.15 (6H, m), 7.10 (1H, s), 6.98 (1H, d, J=7.4 Hz), 6.63 (1H, d, J=7.4 Hz), 4.00-2.70 (8H, m), 2.64 (2H, t, J=7.2 Hz), 2.20-1.85 (4H, m), 1.80-1.50 (4H, m).

15 IR (KBr) : 3219, 2937, 1652, 1538, 1500, 1455, 1291, 1216, 786, 757 cm⁻¹.

Elemental analysis for C₂₆H₃₁Cl₂N₅O₂S·2.5H₂O
Calcd.: C, 52.61; H, 6.11; N, 11.80.
Found : C, 52.88; H, 6.18; N, 11.58.

20 Example 175
Synthesis of N-[1-[3-(4-Aminophenyl)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride
1) Synthesis of N-[1-[3-(4-tert-

25 Butoxycarbonylaminophenyl)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
3-(4-tert-Butoxycarbonylaminophenyl)propyl methanesulfonate (423 mg, 1.28 mmol) was added to a stirred solution of N-(piperidin-4-yl)-5-thia-1,8b-

30 diazaacenaphthylene-4-carboxamide dihydrochloride (400 mg, 1.07 mmol), triethylamine (539 mg, 5.33 mmol), sodium iodide (192 mg, 1.28 mmol) and 1,8-diazabicyclo[5.4.0]undecene (326 mg, 2.14 mmol) in acetonitrile (20 ml) at room temperature. After refluxing under nitrogen for 1 day, the reaction mixture was concentrated in vacuo. The residue was

dissolved in water and extracted with chloroform. The extract was washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (20 g) with Ethyl acetate-Methanol (3:1)

5 to give N-[1-[3-(4-tert-
butoxycarbonylaminophenyl)propan-1-yl]piperidin-4-yl]-
5-thia-1,8b-diazaacenaphthylene-4-carboxamide as purple
amorphous (350 mg, 61%).

10 ¹H-NMR (200 MHz, CDCl₃) δ: 7.40-7.00 (4H, m), 6.80-6.58
(3H, m), 6.45-6.38 (1H, m), 5.79 (1H, dd, J=5.8
and 1.4 Hz), 5.65-5.55 (1H, m), 3.90-3.70 (1H, m),
2.95-2.78 (2H, m), 2.70-2.50 (2H, m), 2.45-2.30
(2H, m), 2.20-1.58 (8H, m), 1.43 (9H, s).

15 2) Synthesis of N-[1-[3-(4-Aminophenyl)propan-1-
y1]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-
carboxamide trihydrochloride

20 Concentrated hydrochloric acid (1.5 ml) was added
to N-[1-[3-(4-tert-butoxycarbonylaminophenyl)propan-1-
y1]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-
carboxamide (350 mg, 0.656 mmol) and the mixture was
stirred at room temperature for 2 hours. Ethanol was
added to the mixture to give N-[1-[3-(4-
aminophenyl)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-
diazaacenaphthylene-4-carboxamide trihydrochloride as
25 orange crystals (251 mg, 71%), which were collected by
filtration and washed with ethanol.

30 ¹H-NMR (200 MHz, DMSO-d₆) δ: 8.80-8.70 (1H, m), 7.59
(1H, s), 7.40-7.15 (6H, m), 6.94 (1H, d, J=9.6
Hz), 6.54 (1H, d, J=7.8 Hz), 4.00-3.20 (3H, m),
3.20-2.80 (6H, m), 2.80-2.60 (2H, m), 2.20-1.80
(6H, m).

IR (KBr) : 3000, 2557, 1653, 1631, 1515, 1498, 1299,
1216, 1116, 823, 782 cm⁻¹.

Elemental analysis for C₂₄H₃₀Cl₃N₅OS•1.5H₂O

35 Calcd.: C, 50.57; H, 5.84; N, 12.29.
Found : C, 50.60; H, 5.77; N, 12.33.

Example 176

Synthesis of N-[1-[3-(3-Aminophenyl)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride

5 1) Synthesis of N-[1-[3-(3-tert-Butoxycarbonylaminophenyl)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide
10 3-(3-tert-Butoxycarbonylaminophenyl)propyl methanesulfonate (423 mg, 1.28 mmol) was added to a stirred solution of N-(piperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride (400 mg, 1.07 mmol), triethylamine (539 mg, 5.33 mmol), sodium iodide (192 mg, 1.28 mmol) and 1,8-diazabicyclo[5.4.0]undecene (326 mg, 2.14 mmol) in acetonitrile (20 ml) at room temperature. After refluxing under nitrogen for 16 hours, the reaction mixture was concentrated in vacuo. The residue was dissolved in water and extracted with chloroform. The extract was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was chromatographed on silica gel (15 g) with Ethyl acetate-Methanol (3:1) to give N-[1-[3-(3-tert-

15 butoxycarbonylaminophenyl)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as a purple amorphous powder(413 mg, 72%).

20

¹H-NMR (200 MHz, CDCl₃) δ: 7.23-7.00 (3H, m), 6.85 (1H, d, J=7.4 Hz), 6.70-6.50 (4H, m), 5.90-5.75 (1H, m), 5.78 (1H, dd, J=5.8 and 1.8 Hz), 4.00-3.75 (1H, m), 3.00-2.80 (2H, m), 2.62 (2H, t, J=7.2 Hz), 2.43 (2H, t, J=7.4 Hz), 2.30-1.55 (8H, m), 1.51 (9H, s).

25 2) Synthesis of N-[1-[3-(3-Aminophenyl)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride

30 Concentrated hydrochloric acid (1.5 ml) was added to N-[1-[3-(3-tert-butoxycarbonylaminophenyl)propan-1-

yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide (392 mg, 0.735 mmol) and the mixture was stirred at room temperature for 1 hour. Ethanol was added to the mixture to give N-[1-[3-(3-

5 aminophenyl)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide trihydrochloride as orange crystals (265 mg, 66%), which were collected by filtration and washed with ethanol.

10 $^1\text{H-NMR}$ (200 MHz, DMSO- d_6) δ : 8.85-8.75 (1H, m), 7.63 (1H, s), 7.50-7.36 (1H, m), 7.32-7.16 (5H, m), 6.96 (1H, d, $J=9.2$ Hz), 6.59 (1H, d, $J=7.4$ Hz), 4.20-3.20 (4H, m), 3.20-2.80 (5H, m), 2.68 (2H, t, $J=6.8$ Hz), 2.20-1.80 (6H, m).

15 IR (KBr) : 3050, 1633, 1567, 1540, 1498, 1307, 1220, 1112, 782 cm^{-1} .

Elemental analysis for $\text{C}_{24}\text{H}_{30}\text{Cl}_3\text{N}_5\text{OS} \cdot 1.5\text{H}_2\text{O}$

Caclcd.: C, 50.57; H, 5.84; N, 12.29.

Found : C, 50.27; H, 5.92; N, 12.05.

Example 177

20 Synthesis of N-[1-[3-(4-Cyanophenyl)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

1) Synthesis of N-[1-[3-(4-Cyanophenyl)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

25 3-(4-Cyanophenyl)propyl methanesulfonate (307 mg, 1.28 mmol) was added to a stirred solution of N-(piperidin-4-yl)-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride (400 mg, 1.07 mmol), triethylamine (539 mg, 5.33 mmol), sodium iodide (192 mg, 1.28 mmol) and 1,8-diazabicyclo[5.4.0]undecene (326 mg, 2.14 mmol) in acetonitrile (20 ml) at room temperature. After refluxing under nitrogen for 14 hours, the reaction mixture was concentrated in vacuo. 35 The residue was dissolved in water and extracted with chloroform. The extract was washed with brine, dried

over MgSO₄ and concentrated in vacuo. The residue was chromatographed on silica gel (20 g) with Ethyl acetate-Methanol (2:1) to give N-[1-[3-(4-cyanophenyl)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as a purple oil (298 mg, 63%).

5 ¹H-NMR (200 MHz, CDCl₃) δ: 7.57 (2H, d, J=8.0 Hz), 7.28 (2H, d, J=8.0 Hz), 7.06 (1H, s), 6.75-6.55 (3H, m), 5.79 (1H, dd, J=6.0 and 1.6 Hz), 5.56 (1H, d, J=7.8 Hz), 3.92-3.70 (1H, m), 2.92-2.75 (2H, m), 2.69 (2H, t, J=7.8 Hz), 2.36 (2H, t, J=7.4 Hz), 2.20-2.02 (2H, m), 2.02-1.88 (2H, m), 1.88-1.76 (2H, m), 1.60-1.40 (2H, m).

10 IR (neat) : 3209, 2943, 2227, 1615, 1540, 1508, 1482, 1286, 1156, 734 cm⁻¹.

15 2) Synthesis of N-[1-[3-(4-Cyanophenyl)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

20 Concentrated hydrochloric acid (1.5 ml) was added to a stirred solution of N-[1-[3-(4-cyanophenyl)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide (298 mg, 0.672 mmol) in ethanol (4.0 ml) at room temperature. After stirring at room temperature for 1 hour, the reaction mixture was concentrated in vacuo to give N-[1-[3-(4-cyanophenyl)propan-1-yl]piperidin-4-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as an orange amorphous powder (324 mg, 93%).

25 ¹H-NMR (200 MHz, DMSO-d₆) δ: 8.85-8.75 (1H, m), 7.79 (2H, d, J=7.8 Hz), 7.62 (1H, s), 7.47 (2H, d, J=7.8 Hz), 7.32-7.10 (2H, m), 6.96 (1H, d, J=9.2 Hz), 6.59 (1H, d, J=7.6 Hz), 4.00-3.20 (3H, m), 3.15-2.90 (2H, m), 2.80-2.65 (2H, m), 2.20-1.90 (4H, m), 1.90-1.80 (2H, m).

30 IR (KBr) : 3037, 2939, 2223, 1633, 1500, 1307, 1220, 1114, 776 cm⁻¹.

Example 178

Synthesis of N-[3-[1-(3-Phenylpropan-1-yl)-2-oxopiperazin-4-yl]propane-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

5 1) Synthesis of N-[3-[1-(3-Phenylpropan-1-yl)-2-oxopiperazin-4-yl]propane-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.58 g, 8.24 mmol) was added to a 10 stirred suspension of 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid (900 mg, 4.12 mmol) and N-hydroxysuccinimide (948 mg, 8.24 mmol) in acetonitrile (10 ml) at room temperature and the mixture was stirred at room temperature for 2 hours. A solution of 4-(3-aminopropan-1-yl)-1-(3-phenylpropan-1-yl)-2-oxopiperazine (1.38 g, 5.01 mmol), triethylamine (459 mg, 4.54 mmol) and 1,8-diazabicyclo[5.4.0]undecene (1.25 g, 8.24 mmol) in acetonitrile (20 ml) was added to the mixture. After stirring at room temperature for 15 20 1 day, the reaction mixture was concentrated in vacuo. The residue was dissolved in water and extracted with chloroform. The extract was washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (60 g) with Ethyl acetate-Methanol (5:1) to give N-[3-[1-(3-phenylpropan-1-yl)-2-oxopiperazin-4-yl]propane-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide as a purple amorphous powder (978 mg, 50%).

30 ¹H-NMR (200 MHz, CDCl₃) δ: 7.40-7.10 (5H, m), 7.02 (1H, s), 6.67 (1H, s), 6.66-6.50 (2H, m), 5.72 (1H, d, J=7.0 Hz), 3.60-3.20 (6H, m), 3.17 (2H, s), 2.75-2.60 (4H, m), 2.53 (2H, t, J=5.8 Hz), 2.00-1.78 (2H, m), 1.78-1.60 (2H, m).

35 IR (KBr) : 3248, 2941, 1639, 1544, 1504, 1482, 1282, 1155, 734 cm⁻¹.

2) Synthesis of N-[3-[1-(3-Phenylpropan-1-yl)-2-

oxopiperazin-4-yl]propane-1-yl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride

Concentrated hydrochloric acid (4.5 ml) was added to a stirred solution of N-[3-{1-(3-phenylpropan-1-yl)-2-oxopiperazin-4-yl]propan-1-yl}-5-thia-1,8b-diazaacenaphthylene-4-carboxamide (954 mg, 2.01 mmol) in ethanol (12.0 ml) at room temperature. After stirring at room temperature for 1 hour, the reaction mixture was concentrated in vacuo to give N-[3-{1-(3-phenylpropan-1-yl)-2-oxopiperazin-4-yl]propan-1-yl}-5-thia-1,8b-diazaacenaphthylene-4-carboxamide dihydrochloride as an orange amorphous powder.

INDUSTRIAL APPLICABILITY

The compound (1) or its salt has an excellent LDL receptor up-regulating, blood-lipids lowering, blood-sugar lowering and diabetic complication-ameliorating activity. Therefore, a pharmaceutical composition containing this compound can be safely useful prophylactic and therapeutic drug for atherosclerosis, hyperlipemia, diabetes, diabetic complications, and so on.

CLAIMS

1. A compound of the formula:

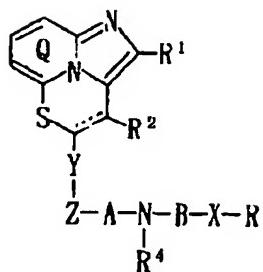


wherein ring Q is an optionally substituted pyridine ring;
one of R⁰, R¹ and R² is -Y⁰-Z⁰, and the other two groups are a hydrogen, a halogen, an optionally substituted hydroxy group, an optionally substituted hydrocarbon group or an acyl group;
Y⁰ is a bond or an optionally substituted divalent hydrocarbon group;
Z⁰ is a basic group which may be bonded via oxygen, nitrogen, -CO-, -CS-, -SO₂N(R³)- (wherein R³ is a hydrogen or an optionally substituted hydrocarbon group), or
-S(O)n- (wherein n is 0, 1 or 2); and
---- is a single bond or a double bond, or a salt thereof.

2. A compound of claim 1, wherein R⁰ is -Y⁰-Z⁰, wherein Y⁰ and Z⁰ are of the same meanings as defined in claim 1.

3. A compound of claim 1, wherein Z⁰ is a group with a molecular weight of not greater than 1000.

4. A compound of claim 1 which is a compound of the formula:



wherein ring Q is an optionally substituted pyridine ring;

A and B independently are an optionally substituted divalent hydrocarbon group which may be bonded via -CON(R^{4a})-, -CO- or -N(R^{4a})-;

X is a bond, oxygen, sulfur, -N(R⁵)CO-, -CO(R⁵)-, -CO- or -N(R⁵)-;

Y is a bond, -CH=CH- or -CH=CH- ;

Z is -CO-, -COO-, -CON(R³)-, -SO₂N(R³)- or -S(O)^m- (wherein m is 0, 1 or 2);

R¹ and R² independently are a hydrogen, a halogen, an optionally substituted hydroxyl group, an optionally substituted hydrocarbon group or an acyl group;

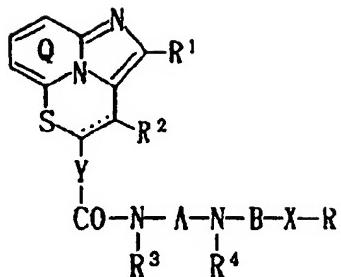
R³, R⁴, R^{4a} and R⁵ independently are a hydrogen or an optionally substituted hydrocarbon group; or

R³ and A, R⁴ and A, R⁴ and B, R⁴ and R⁵, or R⁴ and R may independently be bonded to each other to form a ring;

R is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; and

----- is a single bond or a double bond, or a salt thereof.

5. A compound of claim 1 which is a compound of the formula:



wherein ring Q is an optionally substituted pyridine ring;

A and B independently are an optionally substituted divalent hydrocarbon group which may be bonded via -CON(R^{4a})-, -CO- or -N(R^{4a})-;

X is a bond, oxygen, sulfur, -N(R⁵)CO-, -CO(R⁵)-, -CO- or -N(R⁵)-;

Y is a bond, -CH=CH- or -CH=CH- ;

Z is -CO-, -COO-, -CON(R³)-, -SO₂N(R³)- or -S(O)_m- (wherein m is 0, 1 or 2);

R¹ and R² independently are a hydrogen, a halogen, an optionally substituted hydroxy group, an optionally substituted hydrocarbon group or an acyl group;

R³, R⁴, R^{4a} and R⁵ independently are a hydrogen or an optionally substituted hydrocarbon group; or R³ and A, R⁴ and A, R⁴ and B, R⁴ and R⁵, or R⁴ and R independently may be bonded to each other to form a ring;

R is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; and

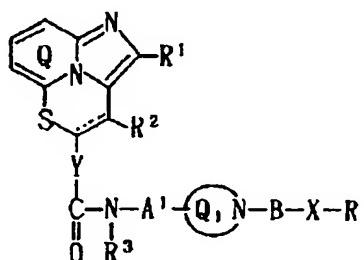
---- is a single bond or a double bond, or a salt thereof.

6. A compound of claim 5, wherein A and B independently are an alkylene group; X is a bond; and

R^3 and R^4 independently are a hydrogen or an optionally substituted alkyl, cycloalkyl, alkenyl, aralkyl or aryl group.

7. A compound of claim 5, wherein ring Q is an unsubstituted pyridine ring; X is a bond; Y is a bond, ---CH=CH--- or ---CH=CH--- ; A and B independently are a C_{1-15} alkylene group; R^1 and R^2 independently are a hydrogen; R^3 and R^4 independently are a hydrogen or a C_{1-15} alkyl, C_{3-8} cycloalkyl, C_{2-18} alkenyl, C_{7-16} aralkyl or C_{6-14} aryl group; and R is a C_{6-14} aryl group.

8. A compound of claim 1 which is a compound of the formula:



wherein ring Q is an optionally substituted pyridine ring;

ring Q_1 is an optionally substituted nitrogen-containing heterocyclic ring;

A' is a bond or an optionally substituted divalent hydrocarbon group which may be bonded via $-CON(R^{4a})-$, $-CO-$ or $-N(R^{4a})-$;

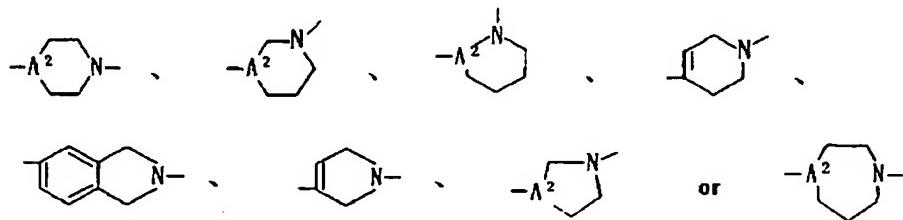
B is an optionally substituted divalent hydrocarbon group;

X is a bond, oxygen, sulfur, $-N(R^5)CO-$, $-CO(R^5)-$, $-CO-$ or $-N(R^5)-$;

Y is a bond, $-\text{CH}=\text{CH}-$ or $-\text{CH}=\text{CH}-\text{C}_6\text{H}_5$;

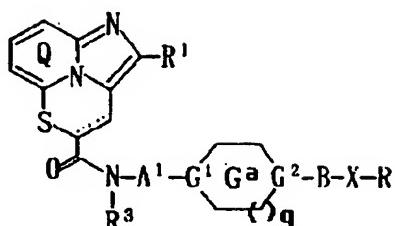
R^1 and R^2 independently are a hydrogen, a halogen, an optionally substituted hydroxy group, an optionally substituted hydrocarbon group or an acyl group; R^3 , R^{4a} and R^5 independently are a hydrogen or an optionally substituted hydrocarbon group; or R^3 and A^1 may be bonded to each other to form a ring; R is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; and ---- is a single bond or a double bond, or a salt thereof.

9. A compound of claim 8, wherein ring Q is an unsubstituted pyridine ring; R^1 and R^2 are a hydrogen; R^3 is a hydrogen or a C_{1-15} alkyl, C_{3-8} cycloalkyl, C_{2-18} alkenyl, C_{7-16} aralkyl or C_{6-14} aryl group; A^1 is (i) a bond, (ii) a C_{1-15} alkylene group which may be substituted by 1 to 3 substituents selected from the group consisting of hydroxy, oxo and phenyl, (iii) a C_{2-16} alkenylene group or (iv) a phenylene group; B is (i) a C_{1-15} alkylene group which may be substituted by 1 to 3 substituents selected from the group consisting of hydroxy, oxo and phenyl, (ii) a C_{2-16} alkenylene group or (iii) a phenylene group; ring Q_1 is a group of the formula:



wherein A^2 is $=\text{C}$ or CH ; X is a bond, oxygen, sulfur or $-\text{CON}(R^5)-$; R^5 is a hydrogen or a C_{1-15} alkyl group.

10. A compound of claim 1 which is a compound of the formula:



wherein ring Q is an optionally substituted pyridine ring;

A¹ is a bond or an optionally substituted divalent hydrocarbon group which may be bonded via -CON(R^{4a})-, -CO- or -N(R^{4a})-;

B is an optionally substituted divalent hydrocarbon group;

X is a bond, oxygen, sulfur, -N(R⁵)CO-, -CON(R⁵)-, -CO- or -N(R⁵)-;

R¹ is a hydrogen, a halogen, an optionally substituted hydroxy group, an optionally substituted hydrocarbon group or an acyl group;

R³, R^{4a} and R⁵ independently are a hydrogen or an optionally substituted hydrocarbon group;

R is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

one of G¹ and G² is N, and the other is CH or N;

ring G^a is an optionally substituted ring;

g is 0, 1 or 2; and

_____ is a single bond or a double bond, or a salt thereof.

11. A compound of claim 10, wherein ring Q is a pyridine ring which may be substituted by 1 to 3 substituents selected from the group consisting of nitro, hydroxy, cyano, carbamoyl, mono- or di-C₁₋₄

alkyl-carbamoyl, carboxy, C₁₋₄ alkoxy-carbonyl, sulfo, halogen, C₁₋₄ alkoxy, phenoxy, naphthoxy, benzyloxy, halophenoxy, C₁₋₄ alkylthio, mercapto, phenylthio, pyridylthio, C₁₋₄ alkylsulfinyl, phenylsulfinyl, C₁₋₄ alkylsulfonyl, phenylsulfonyl, amino, C₁₋₃ acylamino, mono- or di-C₁₋₄ alkylamino, C₁₋₄ alkyl and C₁₋₄ haloalkyl.

12. A compound of claim 10, A¹ is a bond or a C₁₋₁₅ alkylene, C₂₋₁₆ alkenylene group which may be bonded via -CON(R^{4a})-, -CO- or -N(R^{4a})-, wherein R^{4a} is of the same meaning as defined in claim 10.

13. A compound of claim 10, B is a C₁₋₁₅ alkylene or C₂₋₁₆ alkenylene group.

14. A compound of claim 10, X is a bond, oxygen, sulfur, -CONH- or -CO-.

15. A compound of claim 10, R¹ is (1) a hydrogen, (2) a halogen, (3) a hydroxy group which may be substituted by a C₁₋₆ alkyl, phenyl, C₇₋₁₀ aralkyl, formyl, C₁₋₆ alkyl-carbonyl, phenyloxycarbonyl, C₇₋₁₀ aralkyloxy-carbonyl, pyranyl, furanyl or silyl group, (4) a C₁₋₁₅ alkyl, C₃₋₈ cycloalkyl, C₂₋₁₈ alkenyl, C₇₋₁₆ aralkyl or C₆₋₁₄ aryl group or (5) a C₁₋₆ alkoxy-carbonyl, mono-C₁₋₆ alkyl-carbamoyl, di-C₁₋₆ alkyl-carbamoyl or C₁₋₁₀ alkanoyl group.

16. A compound of claim 10, R³ is a hydrogen or a C₁₋₁₅ alkyl, C₃₋₈ cycloalkyl, C₂₋₁₈ alkenyl, C₇₋₁₆ aralkyl or C₆₋₁₄ aryl group.

17. A compound of claim 10, R is (1) a C₁₋₁₅ alkyl, C₃₋₈

cycloalkyl or C₂₋₁₈ alkenyl group which may be substituted by 1 to 5 substituents selected from the group consisting of (i) nitro, (ii) hydroxy, (iii) cyano, (iv) carbamoyl, (v) mono- or di-C₁₋₄ alkyl-carbamoyl, (vi) carboxy, (vii) C₁₋₄ alkoxy-carbonyl, (viii) sulfo, (ix) halogen, (x) C₁₋₄ alkoxy, (xi) phenoxy, (xii) halophenoxy, (xiii) C₁₋₄ alkylthio, (xiv) mercapto, (xv) phenylthio, (xvi) pyridylthio, (xvii) C₁₋₄ alkylsulfinyl, (xviii) C₁₋₄ alkylsulfonyl, (xix) amino, (xx) C₁₋₃ alkanoylamino, (xxi) mono- or di-C₁₋₄ alkylamino, (xxii) 4- to 6-membered cyclic amino, (xxiii) C₁₋₃ alkanoyl, (xxiv) benzoyl and (xxv) 5- to 10-membered heterocyclic group;

(2) a C₇₋₁₆ aralkyl group which may be substituted by 1 to 4 substituents selected from the group consisting of (i) halogen, (ii) C₁₋₄ alkyl, (iii) C₂₋₆ alkenyl, (iv) C₁₋₃ alkanoyl, (v) C₁₋₄ alkoxy, (vi) nitro, (vii) cyano, (viii) hydroxy, (ix) C₁₋₄ alkoxy-carbonyl, (x) carbamoyl, (xi) mono- or di-C₁₋₄ alkyl-carbamoyl and (xii) mono- or di-C₂₋₄ alkenyl-carbamoyl;

(3) a C₆₋₁₄ aryl group which may be substituted by 1 to 4 substituents selected from the group consisting of (i) halogen, (ii) C₁₋₄ alkyl, (iii) C₁₋₄ haloalkyl, (iv) C₁₋₄ haloalkoxy, (v) C₁₋₄ alkoxy, (vi) C₁₋₄ alkylthio, (vii) hydroxy, (viii) carboxy, (ix) cyano, (x) nitro, (xi) amino, (xii) mono- or di-C₁₋₄ alkylamino, (xiii) formyl, (xiv) mercapto, (xv) C₁₋₄ alkyl-carbonyl, (xvi) C₁₋₄ alkoxy-carbonyl, (xvii) sulfo, (xviii) C₁₋₄ alkylsulfonyl, (xix) carbamoyl, (xx) mono- or di-C₁₋₄ alkyl-carbamoyl, (xxi) oxo and (xxii) thioxo; or

(4) a 5- or 6-membered monocyclic heterocyclic group containing 1 to 4 hetero-atoms selected from oxygen, sulfur and nitrogen or a fused bicyclic heterocyclic group containing 1 to 6 hetero-atoms selected from oxygen, sulfur and nitrogen, each of which may be

substituted by 1 to 4 substituents selected from the group consisting of (i) halogen, (ii) C₁₋₄ alkyl, (iii) C₁₋₄ haloalkyl, (iv) C₁₋₄ haloalkoxy, (v) C₁₋₄ alkoxy, (vi) C₁₋₄ alkylthio, (vii) hydroxy, (viii) carboxy, (ix) cyano, (x) nitro, (xi) amino, (xii) mono- or di-C₁₋₄ alkylamino, (xiii) formyl, (xiv) mercapto, (xv) C₁₋₄ alkyl-carbonyl, (xvi) C₁₋₄ alkoxy-carbonyl, (xvii) sulfo, (xviii) C₁₋₄ alkylsulfonyl, (xix) carbamoyl, (xx) mono- or di-C₁₋₄ alkyl-carbamoyl, (xxi) oxo and (xxii) thioxo.

18. A compound of claim 10, wherein ring G^a is a ring which may be substituted by 1 or 2 substituents selected from the group consisting of oxo and C₁₋₆ alkyl.

19. A compound of claim 10, wherein ring Q is an unsubstituted pyridine ring; R¹ and R³ are a hydrogen; G¹ is CH; G² is N; g is 1; and R is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group.

20. A compound of claim 19, wherein ring G^a is unsubstituted ring.

21. A compound of claim 19, wherein A¹ is a bond or a C₁₋₆ alkylene group.

22. A compound of claim 19, wherein A¹ is a bond.

23. A compound of claim 19, wherein B is a C₁₋₆ alkylene group.

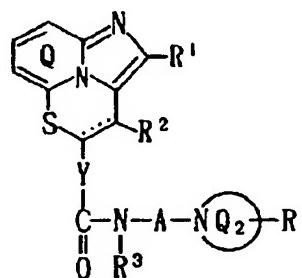
24. A compound of claim 19, X is a bond.

25. A compound of claim 10, ring Q is an unsubstituted pyridine ring; R¹ and R³ are a hydrogen; A¹ is a bond; G¹ is CH; G² is N; ring G³ is a ring which may be substituted by 1 or 2 substituents selected from the group consisting of oxo and C₁₋₆ alkyl; g is 1; B is a C₁₋₆ alkylene group; X is a bond; and R is an optionally substituted phenyl group.

26. A compound of claim 25, ring G³ is unsubstituted ring.

27. A compound of claim 25, wherein R is a phenyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, hydroxy, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy and C₁₋₄ haloalkoxy.

28. A compound of claim 1 which is a compound of the formula:

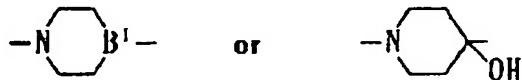


wherein ring Q is an optionally substituted pyridine ring;
 ring Q₂ is an optionally substituted nitrogen-containing heterocyclic ring;
 A is an optionally substituted divalent hydrocarbon group which may be bounded via -CON(R^{4a})-, -CO- or -N(R^{4a})-;

Y is a bond, $-\text{CH}=\text{CH}-$ or $-\text{CH}=\text{CH}-$ ;

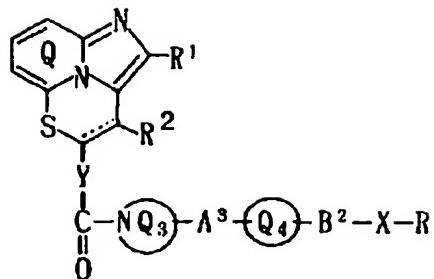
R^1 and R^2 independently are a hydrogen, a halogen, an optionally substituted hydroxy group, an optionally substituted hydrocarbon group or an acyl group;
 R^3 and R^4 independently are a hydrogen or an optionally substituted hydrocarbon group; or
 R^3 and A may be bonded to each other to form a ring;
 R is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; and
 ---- is a single bond or a double bond, or a salt thereof.

29. A compound of claim 28, wherein ring Q is an unsubstituted pyridine ring; R^1 and R^2 are a hydrogen; R^3 is a hydrogen or a C_{1-15} alkyl, C_{3-8} cycloalkyl, C_{2-18} alkenyl, C_{7-16} aralkyl or C_{6-14} aryl group; A is (i) a C_{1-15} alkylene group which may be substituted by 1 to 3 substituents selected from the group consisting of hydroxy, oxo and phenyl, (ii) a C_{2-16} alkenylene group or (iii) a phenylene group; ring Q_2 is a group of the formula:



wherein B^1 is $=\text{C}$, CH or N .

30. A compound of claim 1 which is a compound of the formula:

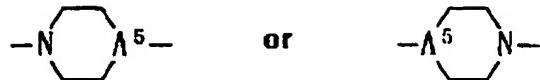


wherein ring Q is an optionally substituted pyridine ring;
 ring Q₃ and Q₄ independently are an optionally substituted nitrogen-containing heterocyclic ring;
 A³ and B² independently are a bond or an optionally substituted divalent hydrocarbon group;
 X is a bond, oxygen, sulfur, -N(R⁵)CO-, -CON(R⁵)-, -CO- or -N(R⁵)-;
 Y is a bond, -CH=CH- or -CH=CH- ;
 R¹ and R² independently are a hydrogen, a halogen, an optionally substituted hydroxy group, an optionally substituted hydrocarbon group or an acyl group;
 R⁵ is a hydrogen or an optionally substituted hydrocarbon group;
 R is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; and
 _____ is a single bond or a double bond, or a salt thereof.

31. A compound of claim 30, wherein ring Q is an unsubstituted pyridine ring; R¹ and R² are a hydrogen; A³ and B² independently are a bond or a C₁₋₁₅ alkylene, C₂₋₁₆ alkenylene or phenylene group; ring Q₃ is a group of the formula:

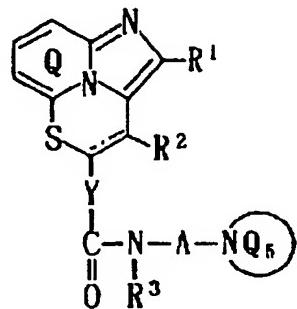


wherein A^4 is $=C$ or CH ; ring Q_4 is a group of the formula:



wherein A^5 is $=C$ or CH .

32. A compound of claim 1 which is a compound of the formula:



wherein ring Q is an optionally substituted pyridine ring;

ring Q_5 is an optionally substituted nitrogen-containing heterocyclic ring;

A is an optionally substituted divalent hydrocarbon group which may be bonded via $-CON(R^{4a})-$, $-CO-$ or $-N(R^{4a})-$;

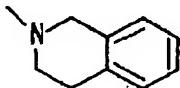
Y is a bond, $-CH=CH-$ or $-CH=CH-\text{[benzene ring]}-$;

R^1 and R^2 independently are a hydrogen, a halogen, an optionally substituted hydroxy group, an optionally substituted hydrocarbon group or an acyl group;

R^3 and R^{4a} independently are a hydrogen or an optionally substituted hydrocarbon group; and

----- is a single bond or a double bond, or a salt thereof.

33. A compound of claim 32, wherein ring Q is an unsubstituted pyridine ring; R¹ and R² are a hydrogen; R³ is a hydrogen or a C₁₋₁₅ alkyl, C₃₋₈ cycloalkyl, C₂₋₁₈ alkenyl, C₇₋₁₆ aralkyl or C₆₋₁₄ aryl group; A is a C₁₋₁₅ alkylene, C₂₋₁₆ alkenylene or phenylene group; ring Q₅ is a group of the formula:



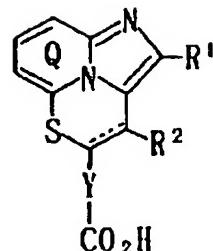
34. A compound of claim 1 which is (R)-N-[1-(1,4-benzodioxan-2-ylmethyl)piperidin-4-ylmethyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide, or a pharmaceutically acceptable salt thereof.

35. A compound of claim 1 which is N-[1-(3-phenylpropyl)piperidin-4-ylmethyl]-3-(5-thia-1,8b-diaza acenaphthylene-4-yl)acrylamide, or a pharmaceutically acceptable salt thereof.

36. A compound of claim 1 which is N-[4-(4-phenylpiperidin-1-yl)butan-1-yl]-5-thia-1,8b-diazaacena phthylene-4-carboxamide, or a pharmaceutically acceptable salt thereof.

37. A compound of claim 1 which is N-[1-(3-phenylpropan-1-yl)piperidin-4-yl]-5-thia-1,8b-diazaacen aphthylene-4-carboxamide, or a pharmaceutically acceptable salt thereof.

38. A process for producing a compound of claim 5, which comprises condensing a compound of the formula:

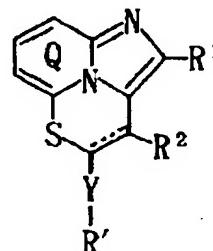


wherein all symbols are of the same meanings as defined in claim 5, or a salt thereof with a compound of the formula:



wherein all symbols are of the same meanings as defined in claim 5, or a salt thereof.

39. A compound of the formula:



wherein R' is an optionally protected COOH, CH₂OH or CHO group; and the other symbols are of the same meanings as defined in claim 4, or a salt thereof.

40. A pharmaceutical composition which comprises a compound of claim 1.

41. A pharmaceutical composition of claim 40, which is an up-regulator of low density lipoprotein receptor.

42. A pharmaceutical composition of claim 40, which is a therapeutic agent for lowering lipids in blood.

43. A pharmaceutical composition of claim 40, which is a therapeutic agent for atherosclerosis.

44. A pharmaceutical composition of claim 40, which is an agent for lowering blood sugar.

45. A pharmaceutical composition of claim 40, which is a therapeutic agent for diabetic complications.

46. Use of a compound of claim 1 for the manufacture of a medicament for lowering lipids in blood.

47. Method for lowering lipids in blood in a mammal which comprises administering to said mammal an effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

Internat. Application No
PCT/JP 97/01395

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D513/06 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 471 236 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 19 February 1992 * entire document *	1-47
A	EP 0 372 445 A (E.I. DU PONT DE NEMOURS AND COMPANY) 13 June 1990 see page 5, line 3 - page 5, line 22; claims 1-6	1-47
A	EP 0 261 439 A (MECT CORPORATION) 30 March 1988 see claims 1-6	1-47
A	EP 0 520 552 A (PIERREL S.P.A.) 30 December 1992 see page 12, line 53 - page 12, line 57; claims 1-17, 32-34	1-47



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *&* document member of the same patent family

1

Date of the actual completion of the international search

16 September 1997

Date of mailing of the international search report

24.09.97

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Authorized officer

Herz, C

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/JP 97/01395

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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EP 372445 A	13-06-90	AU 628890 B AU 4593089 A CA 2003283 A DE 68913667 D DE 68913667 T ES 2063102 T JP 1931585 C JP 2237980 A JP 6062583 B PT 92484 B RU 2028293 C RU 2026292 C US 5166214 A US 5318984 A	24-09-92 07-06-90 05-06-90 14-04-94 14-07-94 01-01-95 12-05-95 20-09-90 17-08-94 09-08-95 09-02-95 09-01-95 24-11-92 07-06-94
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